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Contribution from Indian laboratories to the chemistry of plant products

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Abstract. The review describes chemical work carried out in India on plant products highlighting only those compounds which have novel structural patterns and/or significant biological activity. Contributions mainly in the areas of oxygen heterocycles, terpenoids and alkaloids are discussed.

Keywords. Plant products; oxygen heterocycles; terpenoids; alkaloids

1. Introduction

Organic chemists in India have contributed in an impressive measure to the chemistry of plant products during the past fifty years, a period coeval with the life of the Indian Academy of Sciences. Situated as it is in the tropical and sub-tropical belts of the world, India is endowed with a profusion of plant life, numbering some twenty thousand species of flowering plants, some of which have been in use through the ages for medicinal purposes. It was natural that the chemical investigation of plants became a major area of interest to organic chemists in India. Indeed the amount of chemical work on plants is prodigious and the number of compounds isolated from plants is very large. In this brief review it will only be possible to deal with some of these compounds which have an element of novelty or biological activity and whose structures have been elucidated entirely in this country. There are three major areas in which significant contributions have been made in India *viz* oxygen heterocycles, terpenoids and alkaloids and an attempt will be made to highlight these contributions.

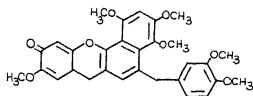
2. Oxygen heterocycles

The late Professor T R Seshadri, working first at Andhra University and later at Delhi University published 1130 papers, most of these on oxygen heterocycles, during a research career spanning forty years. He isolated a large number of flavanoid pigments of Indian plants, both aglycones and glycosides and determined their structures. He carried out extensive synthetic studies to prove the structures assigned on the basis of degradation. In this connection he evolved methods for hydroxylation as well as for removal of hydroxyl groups, methods for partial methylation and demethylation. From flavones and flavanols the methods were extended to isoflavones, chalcones, aurones, isoflavanones, xanthenes and anthraquinones. Methods for the total synthesis of compounds containing C-methyl and C-phenyl groups, furan and chromone rings were also developed. Many other groups of oxygen heterocycles, such as flavandiols, coumarins, chalcones, 2- and 4-phenylcoumarins as well as flavanones,

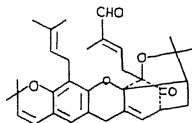
pigment from cotton seed oil served to clear up the confusion which surrounded its structure. Among other complex structures, he solved the structures of santalin A (1) and santalin-B, pigments isolated from *Pterocarpus santalinus* Linn. f. A detailed account of Seshadri's work is presented in a memoir, together with important references (Baker and Rangaswamy 1979).

The late Prof. K Venkataraman, first at the Bombay University Department of Chemical Technology and later at the National Chemical Laboratory, Poona, besides being a leading authority on synthetic dyes contributed extensively to the chemistry of oxygen heterocycles by his work on plant pigments. He elucidated the structures of several of these, such as calycopterin from *Calycopteris floribunda* Lam (Shah and Venkataraman 1942), artocarpin (Dave *et al* 1962) from *Artocarpus integrifolia* Linn. f. and pinoquercetin and pinomyrcetin (Kurth *et al* 1956; Mani *et al* 1956) from *Pinus ponderosa*. Considerable work was carried out on morellin (2), the complex pigment from *Garcinia morella* Desr. whose structure was ultimately solved by x-ray analysis (Karthi *et al* 1963; Madhavan Nair and Venkataraman 1964) as was also that of xanthochymol (Karanjgaokar *et al* 1973; Blount and Williams 1976; Venkatswamy *et al* 1975) from *Garcinia xanthochymus* Hook. f. It is of interest that cambogin (Rogers and Pai, Private Communication) from *Garcinia cambogia* Desr. is enantiomeric with isoxanthochymol. Among unusual flavanoids isolated by his group are chaplashin from *Artocarpus chaplasha* Roxb. and cyclointegrin (3) from *Artocarpus integer* Thunb. Venkataraman contributed greatly in developing methods for the synthesis of flavones and isoflavones. The Baker-Venkataraman transformation provides a convenient route to flavones (Mahal and Venkataraman 1934). The direct conversion of chalcones to flavones was achieved by the use of selenium dioxide (Mahal *et al* 1936). Ethylorthoformate was used for the direct synthesis of isoflavones from desoxybenzoins (Kagal *et al* 1956).

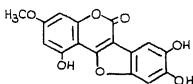
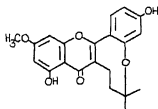
Of the interesting results obtained in the field of oxygen heterocycles from other laboratories may be mentioned the isolation of echiodinin (Govindachari *et al* 1965a), wightin (Govindachari *et al* 1965b) and serpylline (Govindachari *et al* 1968) which gave respectively the unusual 2', 2',3'- and 2',3',4'-oxygenation pattern in the B-ring. Wedelolactone (4) the first representative of the class of coumarano-coumarins was isolated from the medicinal plant *Wedelia calendulaceae* Less and the structures proved



1



2



by degradation and synthesis on classical lines (Govindachari *et al* 1956, 1957; Bowyer *et al* 1957).

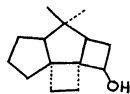
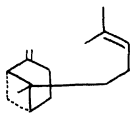
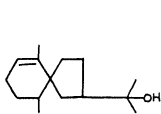
3. Terpenoids

One of the earliest to work on plant products in India was Sir John Lionol Simonson (Jones 1958), who served at the Presidency College, Madras, the Indian Institute of Science, Bangalore, and the Forest Research Institute, Dehra Dun before returning to England. His finding that Δ^3 -carene was the major constituent of Indian turpentine and his isolation of longifolene from *Pinus longifolia* Roxb were important contributions. In England he became one of the leading organic chemists of his generation recognised for his extensive work on the chemistry of terpenoids.

Thanks to the work of schools led by Prof. S C Bhattacharyya and Dr Sukh Dev, the output of work done in India in the field of terpenoids is both notable and extensive. A large number of the economically important essential oils and resin exudates have been examined by these groups in the past three decades. Several hundred new compounds belonging to the sesqui-, di- and triterpenoid classes have been isolated, many of them are of novel types and their structures elucidated.

From fungus-infected agarwood, *Aquillaria agallocha* Roxb. agarospirol (5) α - and β -agarofurans and dihydroagrospirol were isolated and structurally characterised (Maheshwari *et al* 1963). Costus root oil (*Saussurea lappa* C B Clarke) has been intensively studied and several sesquiterpenes with the germacran skeleton have been isolated and characterised. Typical studies are the structure elucidation of dehydrocostus lactone (Mathur *et al* 1965) and the study of the transformation products of costunolide (Joshi *et al* 1966; Hiremath *et al* 1968). (+)-Junenol, canarone and epikhusinol were isolated from the Indian black dammar resin (Hinge *et al* 1965). The structure of bergamotene (6), a novel sesquiterpene, was determined (Kulkarni *et al* 1966). The constituents of North Indian vetiver oil were shown to be distinctly different from those of the oil obtained from other parts of the country, which contain essentially α - and β -vetivones and related compounds. The former is conspicuous by the presence of many antipodal cadinenic and eudesmanic compounds. The major constituent is khusinol (Kalsi *et al* 1963; Kartha *et al* 1963; Rao *et al* 1963; Kelly and Eber 1972). Another constituent is khusiol (7) which is perhaps a precursor of the zizaene type of sesquiterpenes (Ganguly *et al* 1978).

Many novel results have been obtained by Sukh Dev and his collaborators in the field of terpenoids. From *Cedrus deodara* Roxb. several hydrocarbons and alcohols such as α - and β -himachalenes (Joseph and Sukh Dev 1968), himachalol (Bisarya and Sukh Dev 1968a) and allohimachalol (Bisarya and Sukh Dev 1968b) were isolated and their structures established.



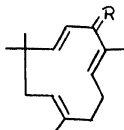
Humulene (8), zerumbone (9), caryophyllene and curcumene were some of the constituents of *Zingiber zerumbat* Smith and all aspects of the structures of the first two compounds were settled (Damodaran and Sukh Dev 1968). The fascinating transformations undergone by the tricyclic longifolene molecule have been the subject of intensive study by Sukh Dev and his group who have also studied in detail the chemistry of isolongifoline (Sukh Dev 1981).

The structures of ishwarone (10) and ishwarane (11) which are rare tetracyclic sesquiterpenes with a novel skeleton were elucidated by Govindachari and coworkers (Govindachari *et al* 1970; Führer *et al* 1970). A number of germacranolides were isolated from *Tithonia tagetiflora* Dept. of which tagitinin F (12) displayed significant anti-cancer activity (Pal *et al* 1976, 1977). Several diterpenes have been isolated from *Coleus forskohlii* Brig. of which the most interesting is coleonol (13) with pronounced hypotensive activity (Bhat *et al* 1977; Tandon *et al* 1977, 1978; Jauhari *et al* 1978). The resin exudate of *Commiphora mukul* (Hook. ex Stocks) has been submitted to detailed chemical examination by Sukh Dev and coworkers. A variety of compounds such as long chain alcohols, lignans, diterpenes and steroids have been isolated and characterised (Patil *et al* 1972, 1973; Prasad and Sukh Dev 1976). There are about ten steroids of which Z and E guggulosterones (14) have marked lipid lowering activity.

Hardwickiic acid (15) is the first simple member of the rearranged labdanes (Misra *et al* 1968).

Cheilanthatriol (16) from the fern *Cheilanthes farinosa* Kaulf. belongs to the rare group of sesterterpenoids (Khan *et al* 1971). Typical of the large number of triterpenoids characterised are the 19-oxygenated oleonane arjunic acid from *Terminalia arjuna* W and A (Row *et al* 1970), the hopane mollugogenol-A from *Molluga hirta* Roxb. (Chakrabarti 1969), and the ursane, lantic acid from *Lantana varama* Linn. (Barua *et al* 1972).

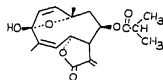
Litsomentol (17) is the simplest member of the cucurbitacin group (Govindachari *et al* 1971) and is exceedingly toxic. Nimbin (18) isolated from the oil of neem



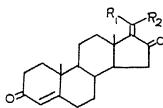
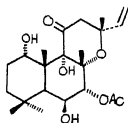
8 R = CH₂
9 R = O



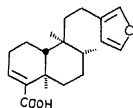
10 R = O
11 R = CH₂



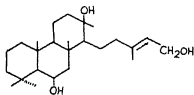
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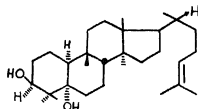
14 Z R = H; E R = CH₃



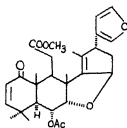
COOH



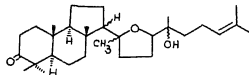
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17



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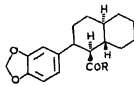
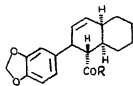
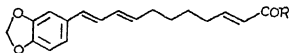
(*Azadirachta indica* A. Juss) represents one of the early examples of a novel type of tetranortriterpenoid (Narayanan *et al* 1964).

Malabaricol (19) isolated from *Ailanthus malabarica* DC represents a new fundamental type of triterpene not encountered before (Chawla and Sukh Dev 1967; Sobti and Sukh Dev 1968).

4. Alkaloids

The great pioneer in the chemical work on plants in India was certainly Prof. S Siddiqui (now settled in Pakistan) who worked at the Tibbia College of Unani Medicine and later at the Board of Scientific and Industrial Research, Delhi. He isolated conessine, conessimine, conessidine from *Holarrhena antidysenterica* Wall. whose bark is used in India for treatment of dysentery (Siddiqui and Pillay 1932, 1934). His work on *Rawvolfia serpentina* Benth ex Kurz whose roots had been used in North India as a sedative led to the isolation of ajmaline, ajmalinine and serpentine (Siddiqui and Siddiqui 1931, 1932, 1935). Siddiqui's publications along with the clinical work of Vakil on *Rawvolfia serpentina* extracts led to a close examination of the plant resulting in the isolation of reserpine, the active principle of the plant with marked hypotensive and sedative activities. These findings created a worldwide interest in the search for medicinal agents from plants, after the Second World War, leading to the isolation of thousands of new compounds of a wide diversity and the development of new techniques of isolation and structure determination. This was the single big factor which enriched organic chemistry in the post-war years.

The medicinal importance of the genus *Piper* has led to the examination of several of its species. Joshi and coworkers isolated from *Piper trichostachyon* C. Dc. four new alkaloids, piperstachine (20), cyclostachine-A (21), cyclostachine-B (22), and cyclopiperstachine (23). The structures were elucidated by a combination of chemical and spectroscopic methods and confirmed by syntheses (Joshi *et al* 1975a; Viswanathan *et al* 1975). Confirmation of the structures of cyclostachine A was obtained by x-ray



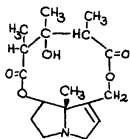
Alder reaction of the amide (24) and cyclopiperstachine from piperstachine. The *cyclo* compounds are not artefacts but exist in the plant. The genus *Crotalaria* is known to produce macrocyclic ester alkaloids incorporating a pyrrolizidine system. Atal *et al* have investigated a large number of plants of the genus and isolated over a dozen new alkaloids. Cromadurine (25) is a typical alkaloid of this group (Rao *et al* 1975). The genus *Ancistrocladaceae* is represented only by one species in India, *Ancistrocladus heyneanus* Wall. A novel group of isoquinoline alkaloids have been isolated from this species. The major alkaloid ancistrocladine has been assigned the structure and stereochemistry depicted in 26. These alkaloids are unique in being the only isoquinoline alkaloids arising from acetate units instead of the usual aromatic amino acids. The chemistry of this group has been reviewed (Govindachari and Parthasarathy 1977).

From *Tiliacora racemosa* colebr (*Menispermaceae*) a number of *bis*-bensylisoquinoline alkaloids were isolated, which are unique in having the isoquinoline moieties joined through a diphenyl unit and not through a diphenyl ether unit as is common. Essential features of the structures of tiliacorine and accompanying alkaloids were established by degradation and synthesis (Anjaneyalu *et al* 1969, 1971). More recently the position of the phenolic hydroxyl group was determined (Shamma *et al* 1976).

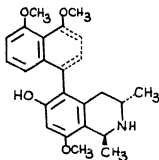
The absolute configuration depicted in 27 was derived using biosynthesis as a tool (Bhakuni *et al* 1978).

More than a dozen alkaloids have been isolated by Bhakuni and coworkers from *Cocculus laurifolius* DC and their structures elucidated (Uprety and Bhakuni 1975; Bhakuni *et al* 1976). Of these isococculidine (28) is a neuromuscular blocking agent. Six bases of the *bis*-benzylisoquinoline type were isolated from *Cocculus pendulus* Forsk and characterised (Bhakuni and Joshi 1975) of which cocculinine (29) displayed anticancer activity.

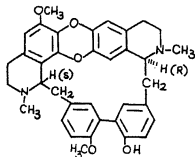
From the leaves of *Murraya koenigii* Spreng, used as a flavouring material for many items of food, almost thirty alkaloids belonging to the carbazole group have been isolated. Chakraborty and coworkers were the first to report the isolation of the alkaloids girinimbine, mahanimbine, and murrayacine. Subsequently, a number of other alkaloids were isolated in other laboratories and there is confusion due to the



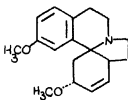
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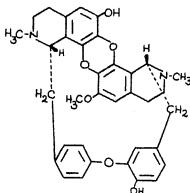
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27



28



29

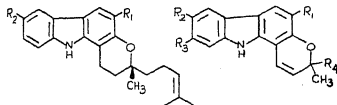
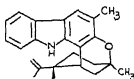
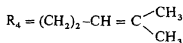
formulated as 30 (Narasimhan *et al* 1968), girinimbine as 31 (Dutta and Quassim 1969), murrayacine as 32 (Chakraborty *et al* 1971), koenimbine as 33 (Kureel *et al* 1969; Joshi *et al* 1970), koenimbidine as 34 (Narasimhan *et al* 1968), isomahanimbine as a position isomer of mahanimbine with the structure 35, mahanine (Narasimhan *et al* 1970) was formulated as 36.

Among the more complex alkaloids, cyclomahanimbine appears correctly constituted as 37 (Bandaranayake *et al* 1974). An x-ray study of murrayazoline (mahanimbidine) has confirmed the structure as 38 (Bordner *et al* 1972).

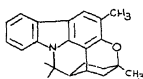
The chemistry of carbazole alkaloids from *M. koenigii*, as well as from other plants of the Rutaceae, has been the subject of two recent reviews (Chakraborty 1977; Joshi 1975).

From the leaves of *Tylophora asthmatica* Wright et Arn used in folk medicine as a cure for asthma, several phenanthroindolizidine alkaloids, the first of this type to be discovered, tylophorine (39), tylophorinine (40), tylophorinidine (41), d-isotylocrebrine (42) and the seco-alkaloid septicine (43) as well as quaternary alkaloids have been isolated. All aspects of the structure and stereochemistry of these alkaloids have been established. Three recent reviews give a detailed account of the chemistry of this group (Góvindhachari and Viswanathan 1978; Wiegrebé 1972; Gellert 1982). All the phenanthroindolizidine alkaloids show significant anti-cancer activity.

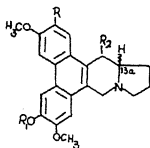
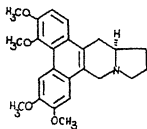
The alkaloids venenatine and isovenenatine (echitovenine) were first isolated from *Alstonia venenata* R.Br. and assigned structures (44) and (45) on the basis of degradation studies. In an admirable thorough study of all parts of *A. venenata*, Chatterjee *et al* have reported the isolation of over twenty new alkaloids. The alkaloids belong to the class of

30 $R_1 = \text{CH}_3$; $R_2 = \text{H}$ 35 $R_1 = \text{H}$; $R_2 = \text{CH}_3$ 31 $R_1 = R_4 = \text{CH}_3$; $R_2 = R_3 = \text{H}$ 32 $R_1 = \text{CHO}$; $R_2 = R_3 = \text{H}$; $R_4 = \text{CH}_3$ 33 $R_1 = R_4 = \text{CH}_3$; $R_3 = \text{H}$; $R_2 = \text{OCH}_3$ 34 $R_1 = \text{CH}_3$; $R_4 = \text{CH}_3$; $R_2 = R_3 = \text{OCH}_3$ 36 $R_1 = \text{CH}_3$; $R_2 = \text{H}$; $R_3 = \text{OH}$ 

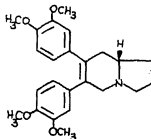
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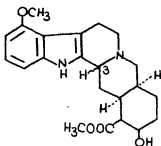
39 $R = \text{OCH}_3$; $\beta\text{-H}$ at 13a $R_1 = \text{CH}_3$; $R_2 = \text{OH}$ 40 $R = \text{H}$; $\alpha\text{-H}$ at 13a $R_1 = \text{CH}_3$; $R_2 = \text{OH}$ 41 $R = \text{H}$; $\beta\text{-H}$ at 13a $R_1 = \text{H}$; $R_2 = \text{OH}$ 

42



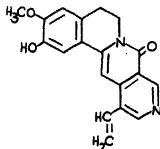
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monoterpenoid alkaloid venoterpine is of great biogenetic significance. The chemistry of the alkaloids of *A. venenata* is the subject of a recent review (Chatterjee *et al* 1978). During the past three decades Prof. (Mrs) Chatterjee and coworkers have investigated over a hundred species of plants, mostly belonging to the *Apocyanaceae* and isolated over fifty alkaloids of the indole group in which most fall into well-recognised categories, some like noreline and grandifoline are of immense complexity whose structures could be solved only.



44 C₃-β-H

45 C₃-α-H



46

Pakrashi's work on *Alangium lammerckii* Thev. besides furnishing several bases of the emetine type has also yielded some alkaloids of novel structures like alangimarine (46) (Pakrashi *et al* 1980) which are 10-azaberberines.

5. Biosynthetic and tissue culture studies on alkaloids

Excellent work has been done for the first time in India, on the biosynthesis of several important alkaloids by Bhakuni and Kapil at the Central Drug Research Institute, Lucknow. Specific incorporation of (+)-reticuline (47) into boldine (48) was demonstrated in *Litsea glutinosa*. The evidence supports the direct oxidative coupling of (+)-reticuline to isoboldine (49) which in turn was a specific precursor for boldine (Bhakuni and Kapil 1974).

The biosynthesis of papaverine (Uprety *et al* 1975), of the bis-benzylisoquinoline alkaloid cocsulinin (Bhakuni *et al* 1978) of the abnormal Erythrina alkaloids cocculidine and cocculine (Bhakuni and Singh 1978), the morphinanandienone alkaloid sebiferine (Bhakuni *et al* 1978) and several others have all been worked out by Bhakuni and coworkers.

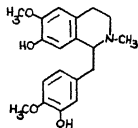
Very interesting tissue culture studies on alkaloid-bearing plants such as *Atropa belladonna* and *Tylophora asthmatica* have been carried out by Chadha *et al* at Bhabha Atomic Research Centre, Bombay, which shed light on the stage of formation of alkaloids in these plants (Eapen *et al* 1978; Benjamin *et al* 1979).

6. Miscellaneous

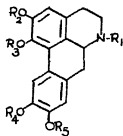
Extensive contributions have been made in India in the field of lignans and glycosides. From the reputed medicinal plant *Picrorhiza kurroa* Benth two C₉ iridoid glycosides picroside (50) and kutkoside (51) were isolated and their structures determined. These compounds are claimed to have hepatoprotective properties (Singh and Rastogi 1972; Rastogi *et al* 1949, 1959).

The cardiac glycoside peruvoside (52) isolated from *Thevetia nerifolia* Juss (Rangaswamy and Venkat Rao 1959; Bisset *et al* 1962) has been shown to be superior to diosgenin and has been marketed in Europe under the name 'Encordin'.

There has been a decline in the investigation of plant products during the past decade and the emphasis has shifted to organic chemical synthesis. However, there is still plenty of scope for work on plant products, using newer techniques of isolation, as well

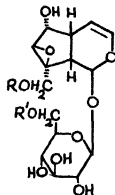


47

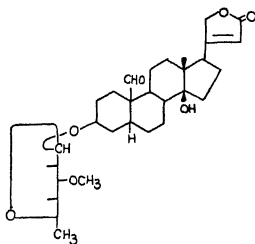


48 $R_1 = R_3 = R_4 = \text{CH}_3$
 $R_2 = R_5 = \text{H}$

49 $R_1 = R_2 = R_4 = \text{CH}_3$
 $R_3 = R_5 = \text{H}$



50 $R = \text{H}$; $R' = \text{cinnamoyl}$
 51 $R = \text{Vanilloyl}$; $R' = \text{H}$



52

as newer analytical methods in structure elucidation. While x-ray analysis can lead to rapid unravelling of structure, it will not contribute to the enrichment of organic chemistry and will serve to dry up the contributions received from the chemical investigation of plant products.

Acknowledgements

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Contributions to organic synthesis and reaction mechanisms

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Abstract. Development of new methods, leading to the first stereo-specific total synthesis of a steroid, *viz* equilenin, and of estrone and their derivatives and of several important synthones, useful for the preparation of physiologically active steroids, and the first conversion of an equilenane to estrane have been described. An account of the achievement of original syntheses of testosterone and its isomers and derivatives and degradation products, urinary steroids, terpenes and their important degradation products has been given. Mechanisms of Dieckmann cyclization, a novel dehydrogenation-addition reaction involving abietic acid and tetrachloro-*o*-benzoquinone, a rearrangement involving a substitution of cyclopentanone-2-carboxylic ester have been elucidated. An abnormal UV absorption exhibited by saturated 1,2-dicyano esters has been rationalized. Divergences in the ORD data of testosterone and 19-nortestosterone from their isomers have been explained by x-ray crystallographic studies of 8-isotestosterone, 8-iso-10-isotestosterone and 8-iso-10-iso-19-nortestosterone. A tentative explanation for the difference in their physiological activities has been suggested.

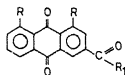
Keywords. Synthesis; steroids; terpenes; reaction mechanism.

1. Introduction

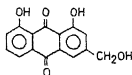
The present article briefly mentions only the significant results of our investigations on the synthesis of natural products, their analogues and degradation products, often physiologically active and mainly in the field of steroids, and studies in reaction mechanisms using physicochemical methods. These investigations have been carried out in the Departments of Organic Chemistry of the University College of Science, Calcutta, the Jadavpur University, Calcutta, the Indian Institute of Science, Bangalore and the University of Wisconsin, Madison, U.S.A.

Our earliest synthetic effort provided (Mitter and Banerjee 1932) the first synthetic confirmation of the structure of aloe-emodin (2), a unique naturally occurring hydroxyanthraquinone, having a carbinol group and the active principle of aloes, rhubarb etc diacetyl rhein (1, b), prepared from rhein (1, a) which had been earlier

CHART I



(1)



(2)

a) $R = R_1 = OH$

b) $R = OAc$; $R_1 = OH$

c) $R = OAc$; $R_1 = Cl$

synthesized (Eder and Widmer 1922) was converted into the aldehyde (1, d) by the Rosenmund reduction of the acid chloride (1, c). The hydroxy aldehyde (1, d) on hydrogenation with Adam's catalyst using ferrous chloride as promoter furnishes aloemodin.

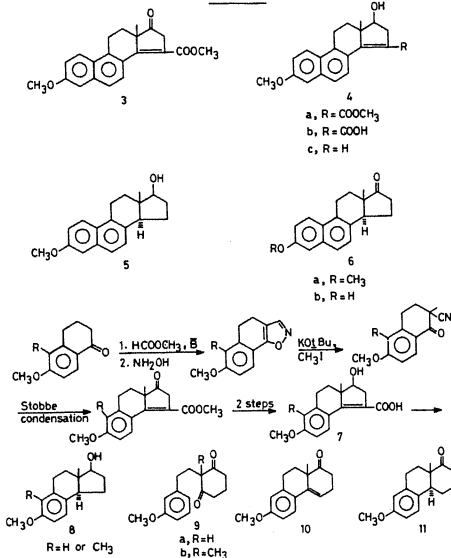
2. Synthesis of equilenanes

2.1 *The first stereospecific synthesis of a natural steroid, equilenin*

The first synthesis of a natural steroid, the female sex hormone, equilenin (*d*-3-hydroxy-17-keto-1,3,5(10),6,8-estrápentaene) (6, b), was achieved by Bachmann *et al* (1939) and this was followed by three other syntheses by Johnson *et al* (1945), Johnson and Stromberg (1950) and Bachmann and Holmen (1951). But, none of these syntheses was stereospecific, more than one racemate being formed during the reaction sequence. However, the first stereospecific synthesis of *d,l*-equilenin methyl ether (6, a), in fact that of any natural steroid because of the earlier conversion of the racemate (6, a) into equilenin (6, b) by Bachmann *et al* (1939, 1940), was reported (Banerjee *et al* 1956) from our laboratory. For this purpose, the tetracyclic unsaturated keto ester (3), earlier prepared by Johnson *et al* (1945), was reduced with sodium borohydride to give the hydroxy unsaturated ester (4, a). Decarboxylation of the corresponding acid (4, b) by heating gave 3-methoxy-17-hydroxy-1,3,5(10),6,8,14-estrahexaene (4, c). Catalytic hydrogenation of 4, c, followed by oxidation of the resulting saturated alcohol (5), afforded *d,l*-equilenin methyl ether (6, a) in an excellent overall yield.

2.2 *Stereospecific synthesis of tricyclic synthones for the steroid synthesis*

The aforementioned method developed for the preparation of the tetracyclic steroid was also employed for the stereospecific synthesis (Banerjee *et al* 1956) of two very important tricyclic *trans*-benzohydrindane synthones (8, R=H and 8, R=CH₃), as outlined in chart 2, which have later found application in the synthesis of a large number of physiologically active, medicinally important natural steroids and their analogues. Although non-stereospecific synthesis (Bachmann and Thomas 1942; Martin and Robinson 1943) of the above benzohydrindanes (8, R=H and R=CH₃) were reported earlier, their configurations had not been proved. Our investigations provided (Banerjee *et al* 1956; Banerjee and Balasubramanian 1958) rigorous proof for the configurations. It may be mentioned here that the benzohydrindane (8, R=CH₃) has been utilized in our laboratory for the first synthesis (Banerjee *et al* 1960) of 8-isotestosterone (91) and for the first time that of an anthrasteroid (93, a) and also the preparation (Banerjee *et al* 1969) of another anthrasteroid (93, b) starting with the benzohydrindane (8, R=H), to be described later. Further, following a series of brilliant investigations, Velluz *et al* (1965) have described in a review the development of syntheses, for the first time, suitable for the industrial steroid hormones and their active analogues, and for most of these preparations they have utilized the optically active benzohydrindane derivatives (8, R=H), prepared by our method, as the starting material; optical resolution was carried out at the stage of the tricyclic hydroxy acid

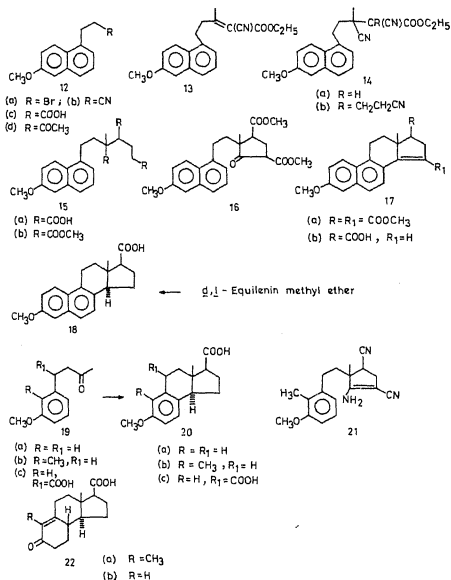


preparation of D-homosteroids. The crude diene (9, b), obtained by the methylation of 2- β -(*m*-methoxyphenyl) ethyl-cyclohexane-1,3-dione (9, a) with potassium ethoxide and methyl iodide, was cyclized with PPA to yield the tricyclic unsaturated ketone (10), which on hydrogenation furnished exclusively *trans*-1-keto-7-methoxy-11-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (11). The *trans*-configuration was proved by degrading it to the ketone obtained by the oxidation of the benzohydrindane (8, R=H).

2.3 Novel synthesis of equilenanes

Later, we have developed two more new routes for the stereospecific synthesis of equilenanes. In the first one (Banerjee *et al* 1961) β -(6-methoxy-1-naphthyl)ethyl bromide (12, a) was converted into the methyl ketone (12, d) via the nitrile (12, b) and the carboxylic acid (12, c). Condensation of the ketone (12, d) with ethyl cyanoacetate gave the unsaturated cyano ester (13). Addition of hydrogen cyanide to 13 afforded the dicyano ester (14, a) which on cyanoethylation furnished the tricyano ester (14, b). Hydrolysis and decarboxylation of 14, b gave the tricarboxylic acid (15, a). The β -ketoester (16) was obtained by Dieckmann cyclization of the triester (15, b), Bougault cyclization of which gave the unsaturated diester (17, a). Saponification of 17, a,

CHART III

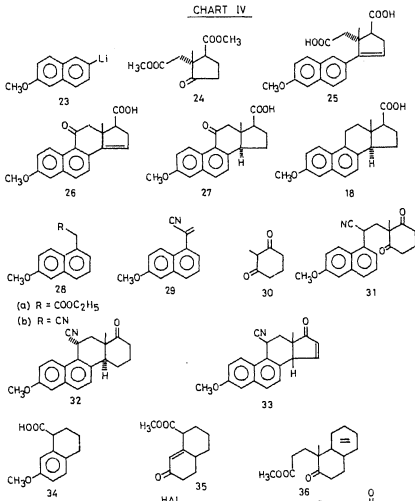


We have utilized (Banerjee *et al* 1961) the above method also for the stereoselective synthesis of three benzohydrindanes (20,a,b and c), useful for the synthesis of steroids, starting from the ketones (19,a,b, and c), as shown in chart III. However the best method for the preparation of the ketone (19,b), among others, was by the Stobbe condensation of the isobutyl enol ether of 2-methyl-dihydroresorcinol (Barnes and Miller 1960) with di-*t*-butyl succinate, followed by heating with Pd-on-carbon to remove the carbo-*t*-butoxy group and aromatize. The resulting 3-methoxy-2-methyl- β -phenylpropionic acid was converted into the ketone (19,b). Again the best method for preparing the benzohydrindane (20,b) from 19,b involved condensation of the latter with *t*-butyl cyanoacetate, addition of hydrogen cyanide and cyanoethylation to obtain a mixture of diastereoisomers, pyrolysis of which to remove the carbo-*t*-butoxyl group, followed by *t*-butoxy-catalyzed Thorpe cyclization of the resulting trinitrile, yielded the two isomeric form of the compound (21). The acid hydrolysis of the mixture of isomers

followed by cyclization with hydrogen fluoride and subsequent alkaline hydrolysis, decarboxylation and hydrogenation furnished the tricyclic acid (20,b) in an excellent overall yield. Birch reduction of the benzohydrindane (20,b) to give the unsaturated keto acid (22,a), identical with the material prepared in connection with Woodward synthesis (Woodward *et al* 1952), provided conclusive proof of the configuration in our series and established an obvious pathway to completion of the steroid synthesis utilizing the Woodward method of attaching ring A. The tricyclic unsaturated keto acid (22,b), obtained in excellent yield from 20,a, is also a valuable synthone for the synthesis of steroids in view of Velluz's experiment (Velluz *et al* 1965).

For the other stereoselective synthesis of the equilenane (18), 2-methoxy-6-lithionaphthalene (23) was condensed with methyl *trans*-2-methyl-3-carbomethoxycyclopentanone-2-acetate (24) (Banerjee and Das Gupta 1952) followed by treatment with Pr₂S and saponification, to obtain 3-methyl-4-carboxy-2-(2'-methoxy-6'-naphthyl)cyclopentene-3-acetic acid (25). Treatment of 25 with phosphorous oxychloride and PPA gave the tetracyclic unsaturated keto acid (26), hydrogenation of which with 5% Pd-charcoal, after absorption of one mole of hydrogen, gave the saturated keto acid (27). Hydrogenation using 30% Pd-charcoal, after absorption of three moles of hydrogen, afforded 3-methoxy-17 β -carboxy-1,3,5(10),6,8-estrapentaene (18). The

CHART IV



identity of the compound was established by a direct comparison with the compound synthesized (Banerjee *et al* 1961) earlier.

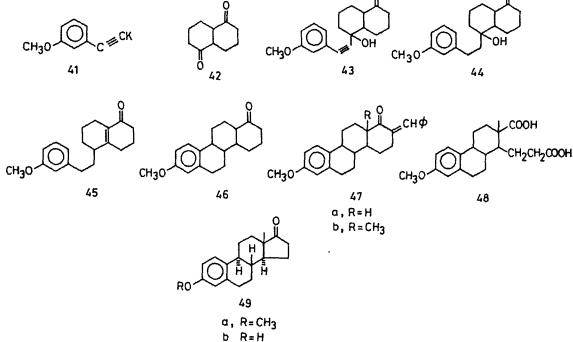
Recently, 11-cyano-D-homoequilenin methyl ether (32) has been prepared (Banerjee *et al* in press) in our laboratory by a novel procedure. 6-Methoxynaphthylacetonitrile (28,b), prepared from the ester (28,a), on treatment with formaldehyde and triton-B, gave the unsaturated nitrile (29), which on condensation with 2-methylcyclohexane-1,3-dione (30) in ethyl acetate and triethylamine furnished the seco-D-Homosteroid (31). Cyclization of 31 with PPA followed by hydrogenation yielded the 11-cyano compound (32). Condensation of 29 with 2-methylcyclopentane-1,3-dione followed by treatment with PPA gave 11-cyano-15-dehydroisoequilenin methyl ether (33) in an extremely poor yield.

In a model study, we had demonstrated (Banerjee *et al* 1960) that the Hagemann ester system (35), distributed in two rings, obtained from 7-methoxy-1,2,3,4-tetrahydronaphthoic acid (34) by Birch reduction and esterification, on alkylation with ethyl β -chloropropionate, treatment with alkali for saponification and removal of the vinylogously reactive β -keto carboxyl, esterification and alkylation with methyl iodide, yielded the compound (36) which might easily be utilized for building the third ring A (steroid) by well-established procedures. It appeared that the application of the results of the model study to the benzohydrindane (40, $n = 1$) and the benzodecalin (40, $n = 2$) would open up a useful route to the steroids and D-homosteroids, and following the method developed (Banerjee *et al* in press) for the preparation of the D-homoequilenin derivative (32), *m*-methoxyatropionitrile (37,a), ethyl *m*-methoxyatropate (37,b) and the cyano halides (38) were condensed (Banerjee *et al* in press) with diones (39,a, and 39,b) and ethyl methyl 3-ketoadipate and the resulting products were further elaborated to afford the tricyclic compounds (40). However, these compounds (40) were invariably obtained as a mixture of *cis*- and *trans*-isomers, with mostly the former predominating. But, the stereoselectively prepared *trans*-tricyclic diacid (20,c, chart 3) is an important synthon in view of our model studies (Banerjee *et al* 1960).

3. Synthesis of estrones

3.1 Synthesis of estrone and its isomers

The first total synthesis of the female sex hormone, estrone (49,b), was realized by Anner and Miescher (1948). The author was associated with Johnson and his group in the achievement (Johnson *et al* 1950, 1951, 1952) of the second synthesis of the hormone (49,b) along with its three stereoisomers, including lumiestrone. The synthetic strategy was as follows. Potassio *m*-methoxyphenylacetylidyde (41) was interacted with decalin-1,5-dione (42) and the resulting isomeric acetylenic carbinol (43) on hydrogenation gave the saturated carbinol mixture (44). Cyclodehydration of either isomer of 44 with aluminium chloride afforded mainly one stereoisomeric form of the tetracyclic ketone (46), whereas the unsaturated ketone (45), obtained by the dehydration of the carbinols (44), gave three forms of the ketone (46), including the one produced directly from 44, by treatment with aluminium chloride. All three were converted into the benzylidene derivatives (47,a), two of those proving to be identical. Two sets of methylated products (47,b), each epimeric at the carbon holding the angular methyl group, were obtained by treatment of the isomeric benzylidene derivatives (47,a) with potassium *t*-butoxide and methyl iodide. Ozonization of each of the methylated

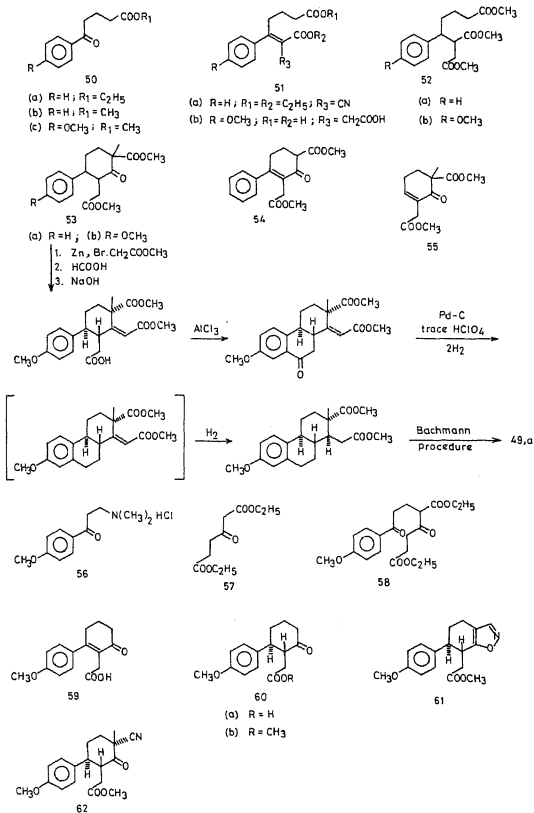


products (47, b) gave four isomers of homomarrrianolic acid methyl ether (48), which on cyclization furnished the corresponding isomers of estrone methyl ether (49, a). Demethylation of the isomeric methyl ethers (49, a) yielded four racemates of estrone (49, b), one of those being identified as that of the natural hormone and another of lumiestrone (Botenandt *et al* 1941).

3.2 The first stereospecific synthesis of estrone

We had realized quite early that the keto diester (53, b) might be an ideal synthone for the synthesis of estrone and we reported (Banerjee and Dutta 1947) the preparation of the keto diester (53, a), as a model, by the following method. Condensation of ethyl γ -benzoyl butyrate (50, a) with ethyl cyanoacetate gave the unsaturated cyanoester (51, a). Reduction of the ethylenic bond of 51, a, condensation of the sodio derivative of the product with ethyl bromoacetate, followed by hydrolysis and esterification, afforded the triester (52, a). Dieckmann cyclization of 52, a and methylation of the resulting β -keto ester furnished the keto diester (53, a). We had also carried out (Banerjee unpublished) Stobbe condensation of 50, b with dimethyl succinate under refluxing condition to obtain the cyclized unsaturated keto diester (54). However, we were anticipated in this approach by Turner (1951), Johnson and Christiansen (1951) and Johnson *et al* (1957). The former, using the shorter Stobbe condensation route, prepared 53, a in the pure crystalline form. The keto diester (53, b) was prepared by both Turner (1951) and Johnson *et al* (1957) by the Stobbe route, in the correct steric form along with another stereoisomer, starting with methyl γ -anisoylbutyrate (50, c) (the ethyl ester was reported earlier (Banerjee 1940)) *via* the unsaturated triacid (51, b). An ingenious method for the preparation of 53, b, as a stereoisomeric mixture, was developed by Bhattacharyya and Sengupta (1952) by the condensation of the unsaturated keto diester (55) with anisole, Protiva *et al* repeated (Jilek *et al* 1953, 1954) Bhattacharyya's experiment and could separate the desired crystalline isomer of 53, b, as the major product. It was Johnson

CHART VI



and coworkers who ultimately converted the keto diester (53,b) stereoselectively to estrone methyl ether (49,a) as schematically shown in chart VI.

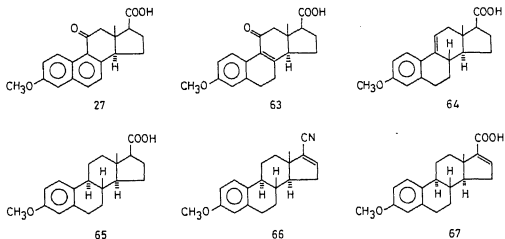
However, none of the reported syntheses of estrone, so far, was stereospecific, and we realized (Banerjee and Sivanandiah 1960) the first such synthesis by devising a new method for the preparation of the keto diester (53,b), which proved to be stereoselective. Condensation of β -dimethylamino-*p*-methoxy- α -naphionphenone hydrochloride (56)

was converted into the unsaturated keto acid (59). Lithium-ammonia reduction of 59 furnished the *trans*-saturated keto acid (60,a). The methyl ester (60,b) was converted, *via* the isoxazole (61) and the methylated keto cyano ester (62), to the required isomer of 53b in an excellent overall yield.

3.3 The first conversion of an equilenane to estrone

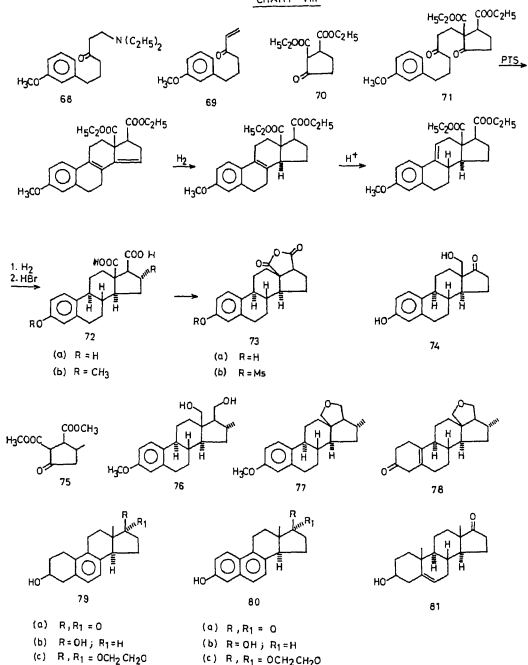
At quite an early date Marker had reported (Marker 1938) the conversion of 17-dihydroequilenin methyl ether to 17 β -estradiol by reduction with sodium and alcohol. However, this claim could not be substantiated (Ruzicka *et al* 1938; Dauben and Ahranjian 1956; Johnson *et al* 1958; Banerjee *et al* 1969; Banerjee and Nadamuni 1969). The first stereospecific conversion of an equilenane, *d,l*-3-methoxy-11-keto-17 β -carboxy-1,3,5(10),6,8-estrapientaene (27, chart IV), to an estrane, *d,l*-3-methoxy-17 β -carboxy-1,3,5(10)-estratriene (65), was reported (Banerjee *et al* 1970) from our laboratory. Simultaneously Birch and Subba Rao had also reported (Birch and Subba Rao 1970) the conversion of *d,l*-3-methoxy-11-17-diketo-1,3,5(10),6,8-estrapientaene to *d,l*-estrone methyl ether. For our conversion, the tetracyclic keto acid (27) was reduced by sodium-ammonia (Mejer and Respondek 1965; Mejer 1962) to the estratetraene (63). Clemmenson reduction of 63 furnished the unsaturated acid (64) which on hydrogenation yielded 17 β -carboxyestrane-3-methyl ether (65). Its structure and configuration were proved by direct comparison with an authentic specimen, prepared from *d,l*-estrone methyl ether (49,a), *via* the unsaturated nitrile (66) and the acid (67).

CHART VII



3.4 Syntheses of urinary steroids

Marrian *et al* (1957) had isolated a urinary steroid metabolite, known as Kober Chromogen KC6A, and its structure was determined (Loke *et al* 1958, 1959) as *d*-18-hydroxyestrone (74). For the synthesis of the above urinary steroid, the method developed by Douglas *et al* (1963) was adopted (Banerjee *et al* 1979 for the synthesis of estrone). Accordingly, the condensation product, the diketo diester (71), obtained by the interaction of the mixture of the Mannich base (68) and the vinyl ketone (69) with ethyl cyclopentanone-2,3-dicarboxylate (70), was put through the steps outlined in chart VIII to



(73,a). Mesylation of 73,a furnished the derivative (73,b). Barton and coworkers had earlier reported (Baldwin *et al* 1968) the multistep conversion of *d*-estrone (49,b) to *d*-18-hydroxyestrone (74), in which the *d*-mesyl anhydride (73,b) was an intermediate towards the end. The solution IR spectra of our racemate (73,b) and of *d*-73,b were superimposable, and thus a formal synthesis of 18-hydroxy-estrone was achieved.

Using ethyl 4-methylcyclopentanone-2,3-dicarboxylate (75) for condensation with the mixture of 68 and 69 and following the same procedure the 16 α -methyl-analogues (72,b, 76, 77 and 78) were prepared.

Another urinary steroid, 3 β -hydroxy-17-keto-5(10),6,8-estratriene (79,a), was isolated by Heard and Hoffman (1940, 1941) and later in larger quantities by Glen *et al* (1958) from the equine pregnancy urine. The former had assigned the structure and configuration (79,a) to it. Considerable interest also centred round this B-aromatic steroid (79,a) because of the postulate (Starka and Brener 1966 a, b; Starka *et al* 1966)

and Harnik (1965) had complicated the issue. For the synthesis (Banerjee and Nadamuni 1969) of 79,a, and its α -epimer and their ketals, *d,l*-equilenin (80,a), *d,l*-dihydroequilenin (80,b) and *d*-equilenin ketal (80,c) were catalytically hydrogenated and in each case two neutral products were obtained in contrast to the observation of Dauben and Ahramjian (1956) that only one was formed in the hydrogenation of *d*-equilenin (80,a). Neutral products, obtained from 80,a,b, were proved to be 3-hydroxyl epimers of the diol (79,b) by their oxidation to epimers of 79,a and by conversion of one of the epimers of 79,a to the other. Our assignment of configuration to the epimers of 79,b and 79,a was based on the studies (Levine *et al* 1963, 1966) on the conformational analysis of reduction products of 5, (10)-unsaturated 3-keto compounds. Similar assignments were made to the epimeric neutral products obtained from the ketal (*d*-80,c). We confirmed the configuration of the urinary metabolite by direct comparison of its ketal (*d*-79,c) with the β -epimer of our synthetic ketal and by the identity of solution IR spectra of the β -acetate of the synthetic *d,l*-79,a and the acetate of the metabolite. This synthesis helped to clear up the confusion existing in the field.

4. Synthesis of androstanes

4.1 Syntheses of 9(11)-dehydrotestosterone and testosterone

Testosterone (*d*-3-keto-17 β -hydroxyandrostane-4-one) (87,a) is the most potent male sex hormone. We have synthesized this hormone and 9(11)-dehydrotestosterone (84), starting with the benzohydrindane synthone (8, R=CH₃), which on lithium-ammonia reduction under specific conditions yielded the unsaturated ketone (82). Hajos *et al* (1966) prepared an optical antipode of 82 by an entirely different route. The *d*-benzoates of 82 and its hydrogenation product (83) were obtained by Hartshorn and Jones (1962) from *d*-testosterone. The solution IR spectra of these degradation products and our synthetic *d,l*-82 and 83 benzoates were superimposable. Condensation of 82 with vinyl methyl ketone furnished *d,l*-9(11)-dehydrotestosterone (84), albeit in poor yield. We had assigned the structure and configuration of 84 on the basis of steric factor, conformational analysis and chromatographic behaviour. The formation of 84 was confirmed by an alternative synthesis by modification of Woodward's method (Woodward *et al* 1952) for building the ring-A. Thus, condensation of the *N*-methylanilinomethylene derivative of 82 with acrylonitrile followed by alkaline hydrolysis gave the unsaturated keto acid (85), whose configuration was proved by comparing its solution IR spectrum with that of a *d*-authentic specimen (Vida and Gut 1965). The acid chloride of 85 was condensed with di-*t*-butyl sodiomalonate and the product successively treated with acetic-monochloroacetic acids and alkali to furnish 84, identical with the earlier product. Further, solution IR spectra, TLC and GLC of our *d,l*-84 were identical with those of a *d*-authentic specimen (Velluz *et al* 1965). Because of the earlier conversion of *d*-84 to cortisone by Velluz *et al* (1960) this also completes a formal synthesis of the latter. The acid chloride of the saturated keto acid (86), obtained by the hydrogenation of 85, was condensed with di-*t*-butyl ethoxymagnesiomalonate and the treatment of the product as before furnished *d,l*-testosterone (87,a). The identity of the

synthetic product and its 2,4-DNP was established by comparison with authentic specimens in the usual way.

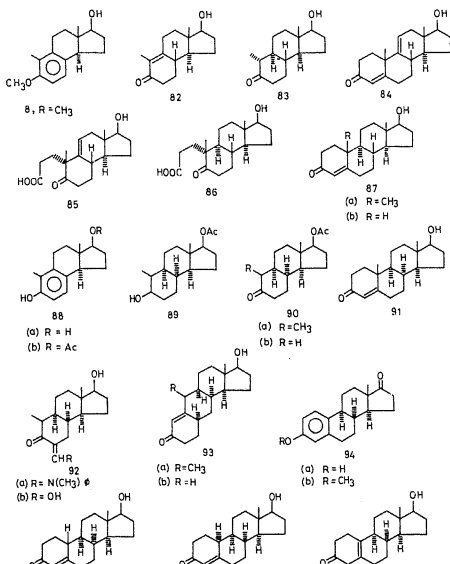
4.2 Syntheses of 8-isotestosterone, anthrasteroids and 8-iso-10-iso-19-nortestosterone

Djerassi *et al* (1957) reported a multi-step conversion of diosgenin to 8-isotestosterone (91), which retained about one half of the biological activity of testosterone (87,a) by the Capon unit test, and its ORD curve was observed to be entirely different from that of testosterone (87,a). The latter fact and model studies led Djerassi to suggest that the ring-B in 91 existed in the boat form. We were the first to achieve (Banerjee *et al* 1960, 1964) the total synthesis of this interesting testosterone isomer; the starting material in this case also was the benzohydrindane (8, R=CH₃). Demethylation of 8, R=CH₃ gave the phenol (88,a). The acetate (88,b) obtained by the partial acetylation of 88,a, was hydrogenated with Ru-C catalyst at a high temperature and pressure to the hydroxy acetate (89) as the major product. Oxidation of 89 furnished the keto acetate (90,a), which on condensation with vinyl methyl ketone yielded stereoselectively *d*,*l*-8-isotestosterone (91). It was also prepared by alkylating the *N*-methylanilinomethylene derivative (92,a) followed by removal of the protecting group. Our assignment of configuration to the condensation product was based on the consideration that the axial alkylation at the methine carbon of 90,a should take place from the convex face of the *cis*-decalin cage and the resulting product could cyclize only by forcing the ring-B into a boat conformation. The solution IR spectra of Djerassi's compound and our synthetic product, taken on different machines, compared well. However, x-ray crystallographic study of our synthetic compound confirmed its structure and configuration and also provided an explanation for the difference in the ORD data of *d*-8-isotestosterone (91) and of *d*-testosterone (87,a), details of which have been described in a later section.

Treatment of the hydroxymethylene derivative (92,b) with vinyl methyl ketone gave a different product, obviously the linear tetracyclic ketone (93,a); this was perhaps the first recorded synthesis of an anthrasteroid. The lower homologue (93,b) was also similarly prepared (Banerjee *et al* 1968, 1969), *via* the keto acetate (90,b), starting with the benzohydrindane (8, R=H). Velluz *et al* (1963) had claimed the preparation of *d*-8-iso-19-nortestosterone (*d*-95) by direct condensation of vinyl methyl ketone with the *d*-keto acetate (90,b) which they had prepared from the benzohydrindane (*d*-8, R=H) following the published steps (Banerjee *et al* 1960) for the preparation of 90,a from 8, R=CH₃. However, considering the enolizability of the methine hydrogen at C-10 due to vinylogy and the strain imposed because of the boat shape (Djerassi *et al* 1957) of the ring-B in 8-iso-19-nortestosterone, the possibility of the obtention of the all-chair shaped *d*-8-iso-10-iso-19-nortestosterone (96) by Velluz *et al* (1963) in the above condensation could not be ruled out. This necessitated an unambiguous synthesis of *d*-96, which was accomplished by us (Banerjee *et al* 1968, 1969). In the hydrogenation of the ethylene ketal of *d*-equilenine (80,c) we had obtained (Banerjee *et al* 1968, 1969) besides the two neutral products, after deketalization, *d*-8-isoestrone (94,a) as one of the two phenolic products. Birch reduction of the methyl ether (*d*-94,b), followed by treatment with methanolic hydrochloric acid and inverted dry column chromatography of the product, gave the α,β -unsaturated keto alcohol (*d*-96) as the minor

the $\beta\gamma$ -unsaturated keto alcohol (*d*-97), also obtained by Velluz *et al* in their condensation reaction. Direct comparison showed that *d*-96 was identical with the product claimed as *d*-8-iso-19-nor-testosterone (*d*-95) by Velluz *et al* (1963). In the meanwhile, Bucourt *et al* (1968) had revised the configuration of their product, but claimed also the formation of 8-iso-19-nortestosterone in very small quantity. A comparison of the ORD curves of testosterone (87,a) and 19-nortestosterone (87,b), 8-iso-10-isotestosterone (154) and 8-iso-10-iso-19-nor-testosterone (96) and 8-isotestosterone (91) and 8-iso-19-nortestosterone (95) showed that while the curves of the former two pairs were very similar, curves of the last pair were quite different, and we concluded (Banerjee *et al* 1968, 1969) that the product obtained second time by Bucourt also could not be *d*-8-iso-19-nortestosterone (95). But, later they provided (Bucourt *et al* 1969) irrefutable evidence in favour of their assignment. More recently, this divergence in the ORD curves of *d*-91 and *d*-95 could be explained through our x-ray crystallographic studies of *d,l*-8-isotestosterone (91), which forms the subject matter of a later section.

CHART IX

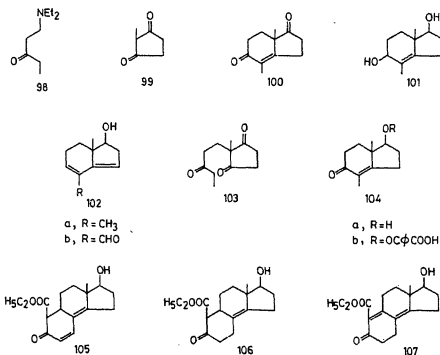


Recently, we reported (Banerjee *et al* 1976) the synthesis of a bicyclic synthon, the hydroxy diene aldehyde (102,b) with the expectation that it might be useful for the synthesis of steroids. For its preparation, the Mannich base (98) was condensed with 2-methylcyclopentane-1,3-dione (99) to give the enedione (100). The diol (101), obtained by the reduction of 100 with sodium borohydride, on dehydration furnished the dienol (102,a), oxidation of which with selenium dioxide yielded the hydroxy diene aldehyde (102,b).

For the synthesis of natural steroids, we have now prepared (Banerjee *et al* 1984) the required optical antipode of 102,b. For this purpose, the triketone (103) was cyclized using *d*-valine as the chiral catalyst to obtain the optically active enedione (100) in high chemical and optical yield. The optical purity of the above product was determined by the chemical resolution of the monophthalate (104,b) of the hydroxy unsaturated ketone (104,a) obtained by the selective reduction of the racemic enedione (100). ORD and NMR chiral LSR studies corroborated the results of chemical resolution. The optically active 100 was put through the steps, mentioned earlier, to afford the required optically active 102,b.

To investigate the steps for the development of a method for the synthesis of steroids, the racemic 102,b has been condensed with ethyl acetoacetate to obtain the tricyclic hydroxy diene keto ester (105), hydrogenation of which has afforded the hydroxy β,γ -unsaturated keto ester (106). Currently, work is in progress to oxidize 106 to the hydroxy diene keto ester (107), the suitable elaboration of which is expected to lead to a stereoselective synthesis of steroids.

CHART X



5. Synthesis of terpenes

5.1 Total synthesis of valeranone

The structure and absolute configuration of the non-isoprenoid sesquiterpene ketone, valeranone (114), the first of a unique group of ketones with two angular methyls, were elucidated due to efforts of several groups of workers and confirmed by three different syntheses by two groups, viz Marshall *et al* (1965, 1968) and Wenkert and Berges (1967) starting from 1-carvomenthone and *d*-carvomenthone respectively. We reported (Banerjee and Angadi 1973; Banerjee 1972) a total synthesis of *d,l*-valeranone (114), starting with 9-acetoxy-10-methyl- Δ^4 -octalone-3 (108). Conjugate addition of methylmagnesium iodide to 108 gave the keto acetate (109) with the angular methyls. Condensation of diethyl carbonate with 109 in the presence of sodium hydride furnished the ethoxycarbonyloxy β -keto ester (110). Reduction of 110, *via* its thioketal, afforded ethoxycarbonyloxy ester (111), which on treatment with an excess of methyl lithium yielded the diol (112). Oxidation of 112 yielded the ketol (113), dehydration of which and subsequent hydrogenation gave a mixture of *d,l*-valeranone and one of its isomers; the former was identified by vpc analysis.

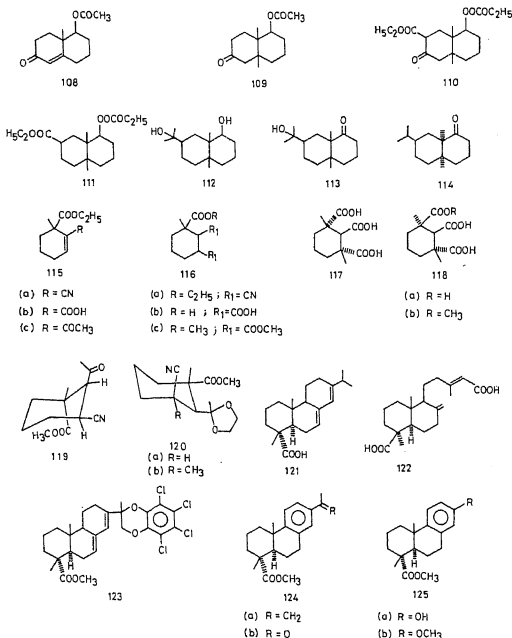
5.2 Syntheses of isomeric C-11 acids—Degradation products of abietic and agathic acids

The elucidation of the structure and configurations, (117) and (118,a), of the isomeric C₁₁-acids, has played a crucial role in the diterpene chemistry (Simonsen and Barton 1952). The *trans*, *meso*-configuration (117) of the optically inactive isomer, obtained (Ruzicka *et al* 1925) first from abietic acid (121), was established by a study (Barton and Schmeidler 1948, 1949) of the dissociation constant of its partial esters. The *cis*, *trans*-configuration (118,a) of the other isomer, derived from agathic acid (122), was assigned (Ruzicka and Bernold 1941) on the basis of the optical activity of its ester. The only published attempt (Schapschinskaya and Arbusov 1935) at a synthesis of these important degradation products recorded that a non-crystalline product, assumed to be a mixture of compounds, was obtained. The first synthesis of these isomeric C-11 acids (117 and 118,a) was accomplished (Banerjee *et al* 1966), the latter by two different routes. Two of the four possible isomers of the precursor triester (116,c), obtained by the addition of hydrogen cyanide to the unsaturated cyanoester (115,a) followed by hydrolysis to the triacid (116,b) and its esterification, on individual methylation using triphenylmethyl sodium gave the *trans*, *meso*-acid (117), identified by comparison with an authentic sample and the *cis*, *trans*-form (118,a) whose structure and configuration were proved by comparison with a specimen obtained by our unambiguous and highly stereoselective second synthesis. This demonstrated that the methylation of isomeric precursor triesters occurred stereospecifically and exclusively at C-3. Stereoelectronic considerations supported the assigned configurations. The second sequence started with the unsaturated keto ester (115,c), obtained from 115, a by hydrolysis followed by conversion of the acid chloride of the derived acid (115,b) through the malonic ester synthesis. Definite conformations to the three key intermediates (119, 120,a and 120,b), obtained during the hydrogen cyanide addition, ketalization and methylation sequence in the transformation of 115,c to the *cis*, *trans*-triacid (118,a), could be assigned from the analysis of their NMR spectra. The furfurylidene derivative of the deketalized 120,b

5.3 A new synthesis of a tricyclic synthone for the terpene and steroid synthesis from abietic acid

Methyl 13-hydroxydeisopropyldehydroabietate (125,a), derived earlier by two groups (Burgstahler and Worden 1961; Wenkert *et al* 1961) from abietic acid in a very low overall yield involving a large number of steps, is considered a useful synthone in the field of synthetic terpenes and steroids. We could synthesize (Banerjee *et al* 1968) 125,a by a novel shorter route in a considerably more improved yield. The adduct (123), formed in an excellent yield by heating the methyl ester of abietic acid (121) with two moles of tetrachloro-*o*-benzoquinone in xylene, on being heated in vacuum gave the styrene derivative (124,a) along with methyl dehydroabietate and tetrachlorocatechol. Ozonolysis of the above mixture, which was more expedient, or of the purified 124,a

CHART XI



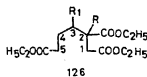
furnished the ketone (124,b), which on Bayer-Villiger oxidation with perbenzoic acid yielded the phenol ester (125,a), identical with an authentic specimen (Wenkert *et al* 1961). Methylation of 125,a furnished the methyl ether (125,b).

The mechanism of the formation of the adduct (123) and its decomposition have been described later.

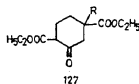
6. Studies in reaction mechanisms

6.1 Studies in the mechanism of Dieckmann cyclization

Apparently contradictory observations of Dobson *et al* (1909) and Chatterjee *et al* (1940) led us to study the mechanism of Dieckmann cyclization of polyesters. The former group cyclized (Dobson *et al* 1909) diethyl β -ethoxycarbonylpimelate (126,a) with sodium in benzene and hydrolyzed and decarboxylated the resulting β -keto ester to obtain cyclohexanone-3-carboxylic acid (129,a). Sen and Bagchi (1958) proved that the intermediate β -keto ester was mainly 128,a and not 127,a as proposed by Perkin and coworkers. Chatterjee *et al* (1940) had isomerized ethyl 2-ethoxycarbonylcyclopentanone-2-acetate (130,a) to ethyl 5-ethoxycarbonylcyclopentanone-2-acetate (130,b) by treating the former with an ethanolic solution of sodium ethoxide (1.1 mole). Following Openshaw and Robinson (1937) Chatterjee *et al* (1940) suggested that the β -keto ester (130,a) underwent ring fission to form the triester (126,a) which cyclized to yield the isomeric β -keto ester (130,b). Chakravarthi (1953) put forward an absurd mechanism to explain this transformation. Banerjee *et al* (1957) repeated the studies of both Perkin and Chatterjee and found them to be correct. In order to find out whether the β -keto ester (130,a), had opened up by the attack of the base following the mechanism (131) to form the anion (133) which could pick up a proton to form the triester (126,a) and the latter cyclizing through the attack by its C-5 methylene anion on the C-2 ester carbonyl to form the β -keto ester (130,b), we subjected β -acetyl- β -ethoxycarbonylpimelate (126,b) to the treatment under Chatterjee's condition because 126,b should also give rise to the anion (133) under the influence of a base by the mechanism (132) and we found that the β -keto ester (130,b), also in this case, along with ethyl acetate, was formed. The triester (126,a) also gave 130,b under Chatterjee's condition. One observable difference in the two conditions of the reaction was that while the availability of the base in quantity was there under Chatterjee's condition, it was very low under the nonhomogeneous condition of Perkin because of the use of benzene as the solvent. We treated the ethanolic solution of the triester (126,a) with a quarter mole of sodium ethoxide for a short period and obtained the cyclohexane β -keto ester (128,a) as the major product in the β -keto ester fraction, but, when the same mixture was treated for a prolonged period, permitting equilibrium to be attained, the cyclopentane β -keto ester predominated. Kinetic studies by Reed and Thornley (1954) and Carrick and Fry (1955) agreed with the accepted mechanism (Ingold 1953) of Dieckmann cyclization as consisting of four stages, as shown in chart XII. They showed that the reaction in an ethanolic solution of an excess of sodium ethoxide was reversible and unimolecular and that the step-2 for C-C bond formation was rate-determining. They also showed that in a solvent of low dielectric constant the reaction was bimolecular and the step-1 was rate-determining. There are four different ways for the



- (a) $R, R_1 = H$
 (b) $R = COCH_3; R_1 = H$
 (c) $R = CH_3; R_1 = H$
 (d) $R = CH_3; R_1 = COOC_2H_5$



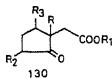
- (a) $R = H$
 (b) $R = CH_3$



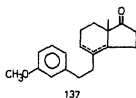
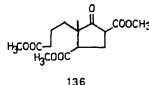
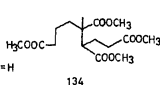
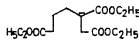
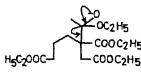
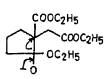
- (a) $R = H$
 (b) $R = CH_3$



- (a) $R, R_1 = H$
 (b) $R = H; R_1 = CH_3$
 (c) $R = CH_3; R_1 = H$



- (a) $R = COOC_2H_5; R_1 = C_2H_5; R_2, R_3 = H$
 (b) $R, R_3 = H; R_1 = C_2H_5; R_2 = COOC_2H_5$
 (c) $R, R_1, R_2, R_3 = H$
 (d) $R, R_2, R_3 = H; R_1 = CH_3$
 (e) $R = CH_3; R_1 = C_2H_5; R_2 = COOC_2H_5; R_3 = H$
 (f) $R = CH_3; R_1, R_2, R_3 = H$
 (g) $R = CH_3; R_1 = C_2H_5; R_2, R_3 = COOC_2H_5$
 (h) $R = CH_3; R_1, R_2 = H; R_3 = COOH$

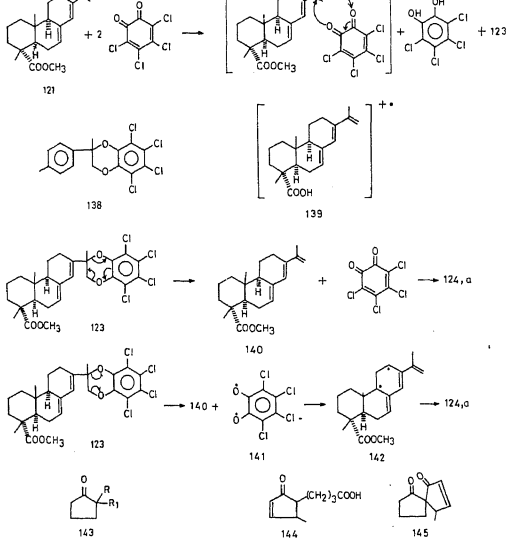


anion attacking the C-2 ester carbonyl (iv) C-2 methine anion attacking the C-5 ester carbonyl; the last possibility, however, cannot be considered because the resulting β -keto ester cannot stabilize itself by enolization at the stage-4 of the reaction. Further, the C-1 methylene being the part of a succinic ester moiety is more acidic than the other two. In view of the above considerations, under Perkin's condition, *i.e.* low availability of the base in the benzene solution, the reaction is bimolecular (Reed and Thornley 1954) and the anion from the most acidic C-1 methylene is predominantly formed and as the stage-2 is faster than the rate-determining stage-1, conversion of the C-1 anion to the cyclized anion is faster than its formation and is continuously removed. This coupled with the low solubility of the sodium enolate in benzene at the last stage yield the cyclohexane β -keto ester (128,a) as the major product; however, the formation of the other two β -keto esters (130,b and 127,a) in small quantities is also possible. Under Chatterjee's condition the reaction is unimolecular and the second step is rate-determining, resulting in the accumulation of the anions which are always in equilibrium with the triester (126,a). Further, all steps being reversible in the homogeneous solution an equilibrium is reached, with comparatively the most stable or the acidic enolate predominating. The greater stability of the cyclopentanone enolate compared to that of cyclohexanone is known from the work of Brown *et al* (1954) and therefore the predominant formation of the cyclopentane β -keto ester (130,b) is to be

28,a) to the cyclopentane β -keto ester (130,b) by treatment with sodium ethoxide and *vice versa* by prolonged treatment with sodium ethoxide in benzene convincingly proved our mechanistic considerations. In all these experiments, the β -keto esters (128,a and 130,b) were identified by the preparation of purified derivatives of the keto acids (129,a and 130,c). The possibility of the crude acids being the mixture of the two with one or the other predominating was proved by the IR spectra of their esters (129,b and 130,d), which showed the product under Perkin's condition to be 80% of 129,b and 20% of 130,d and the product under Chatterjee's condition to be 90% of 130,d and 10% of 129,b. We had also studied (Chakravarty and Banerjee 1946) the cyclization of diethyl β -methyl- β -ethoxycarbonylpimelate (126,c) with sodium and benzene. In this case also there was the possibility of the formation of three β -keto esters (127,b 128,b and 130,e), but hydrolysis and decarboxylation of the product furnished a single crystalline keto acid, identified as 2-methylcyclopentanone-2-acetic acid (130,f) by direct comparison with an authentic specimen (Chakravarty and Banerjee 1946). Exclusive formation of the cyclopentane ring in this case under Perkin's condition is due to three factors, (i) reduction of the acidity of the C-1 methylene due to the electron release effect of the C-2 methyl (ii) steric hindrance to the approaches of the C-5 methylene anion to the carbonyl of the C-1 ethoxycarbonyl and *vice versa* because of the C-2 methyl (iii) comparatively greater proximity of the reaction sites, *viz.* C-5 methylene and the C-2 ethoxycarbonyl, as shown by the model. We have utilized the aforementioned result and considerations for the unique cyclizations of other polyesters (126,d and 134) to obtain synthones useful for our synthetic work. Thus, the tetraester (126,d) on treatment with sodium and benzene gave the cyclopentane β -keto ester (130,g), which on hydrolysis and decarboxylation afforded the *trans*-keto diacid (130,h), unambiguous proof having been provided for its structure and configuration. The use of the dimethyl ester (24) for a new stereospecific synthesis of an equilenane and for the first conversion of an equilenane to the estrane molecule has been described earlier. Another tetraester (134), on treatment with an excess of sodium hydride and benzene, followed by hydrolysis and decarboxylation gave the *cis*-hydrindandione (135) which we considered a useful synthon for steroids. When the tetraester (134) was treated with one equivalent of the base, the cyclopentane β -keto ester (136) resulted (Banerjee and Shafer 1950), adequate proof being provided for its formation. This also demonstrated the priority of the formation of the five-membered ring. To utilize the synthon (135) for the synthesis of estrone, we had condensed (Banerjee and Venkataramu 1974) it with *m*-methoxyphenylethylmagnesium bromide, cyclohexane carbonyl being preferentially attacked, and dehydrated the resulting product to the mixture of the double bond isomers of the unsaturated ketone (137) which on ring closure gave a product to which a spiro structure has been tentatively assigned.

2 A novel dehydrogenation—addition reaction involving abietic acid and tetrachloro-*benzoquinone*

With the view to converting the methyl ester of abietic acid (121) to methyl tetrahydroabietate we had treated (Kasturi *et al* 1966) the former with tetrachloro-*benzoquinone* (1 mole) in xylene, but obtained the solid ester (123) in 41% yield. Alkaline hydrolysis gave the corresponding acid, as it reformed the ester (123) by treatment with diazomethane. Hydrogenation of 123 gave the tetrahydro derivative. The



(a) $R = \text{COOC}_2\text{H}_5$; $R_1 = \text{CH}(\text{CH}_3)\text{CH} = \text{CHCOOC}_2\text{H}_5$

(b) $R = \text{H}$; $R_1 = \text{CH}(\text{CH}_3)\text{CH} = \text{CHCOOH}$

presence of chlorine in and the UV spectrum and the molecular weight of 123 indicated that this could be an adduct. A thorough study of the UV, IR, NMR and mass spectral data confirmed the structure as 123, which could also be converted into the corresponding dehydroabietic acid derivative by treatment with chloranil. Its formation was rationalized by the dehydrogenation-addition sequence shown in chart XIII. The increase in the yield of the adduct to 80 % by using two moles of the quinone for one mole of methyl abietate lends support to it. Further, similar treatment of limonene gave the addition compound (138) which was also obtained from *p*-cymene. This seems to be a general method for functionalization of an iso-propyl group attached to an aromatic ring or adjacent to an ethylenic linkage. In fact, obtention of the adduct (138) from limonene and the appearance of the prominent mass radical ion (139) in the mass spectrum of the abietic acid adduct led us to study the thermal decomposition of the adduct (123) which yielded a mixture of the styrene derivative (124,a) and methyl dehydrabietate. One of the two mechanisms outlined in chart 13, to explain the formation of pyrolysis products consists of the reversal of the adduct formation at the high temperature followed partly by dehydrogenation of the triene (140) with the generated quinone to give the styrene (124,a) and the hydroquinone and partly by the rearrangement of 140 to give methyl

up the hydrogen radicals from the allylic hydrogen atoms in 140 to form the intermediate (142) which might give rise to 124,a. During this study, it was observed that both the aromatic and C-O stretching bands in the IR spectra of polyhalophenols and their ethers were shifted to lower frequencies. It has been shown (Banerjee *et al* 1971) that while the shift of the former is due to the inductive effect of the halogen substituents, the latter has been demonstrated to be due to overcrowding by the halogen atoms.

6.3 *Studies in the mechanism of a rearrangement involving a substitution of cyclopentanone-2-carboxylic ester*

As a model for the introduction of the bile acid side chain by the condensation of ethyl 4-bromo-2-pentenoate with a suitable cyclopentane β -keto ester derivative followed by hydrolysis and decarboxylation, we had condensed (Banerjee and Kasturi 1957) the unsaturated bromoester with 2-ethoxycarbonylcyclopentanone to obtain the substituted keto ester (143,a). Herz (1956) had shown earlier that such condensation products, after reduction, on treatment with concentrated hydrochloric acid yielded rearranged products. We treated the unsaturated keto ester (143,a) under Herz's condition and obtained a mixture of the rearranged cyclopent-2-enone acid (144) and the normal product (143,b), which were characterized by their UV spectra as well as those of their 2,4-DNP. Herz had not reported the formation of any normal product in his experiment. We, however, found that when the condensation product (143,a) was treated with a more dilute acid, *viz* 10% sulphuric acid, the normal product (143,b) could be obtained in 93% yield. Herz had explained the rearrangement through the intermediacy of a spiro diketone of the type (145), a mechanism for which was suggested by Ramirez and Paul (1955) on the basis of the mechanism proposed by Dewar (1949). This, however, cannot explain the formation of the normal product by the treatment with a dilute acid. We proposed (Banerjee and Kasturi 1957) that the spiro diketone (145) was formed by the attack of the dioxycarbonium ion, formed from the carboxylic group of 143,b, on the keto methine, followed by the elimination of proton, because such dioxycarbonium ions are formed only in the presence of strong acids. Later, 145 could open both ways to give rise to the mixture of rearranged and normal products (144 and 143,b).

6.4 *Studies in the UV absorption of saturated dicyano esters*

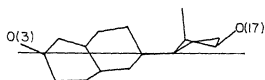
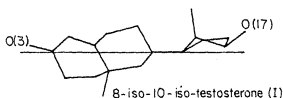
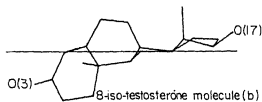
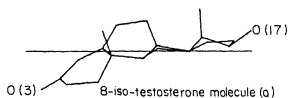
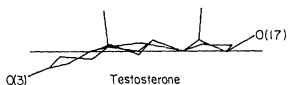
In connection with the synthesis of steroid degradation products, we added (Banerjee *et al* 1957) hydrogen cyanide to the unsaturated cyano ester (146) with UV (ethanol) 235 nm ($\log \epsilon$ 4.0) characteristic of an α,β -unsaturated cyano ester. We checked the UV of the crude addition product, the dicyano ester (147) to find out whether the addition had gone to completion. Although the product was free from the 235 absorption band, it showed a new one at 247 ($\log \epsilon$ 3.6). Later, Kasturi *et al* (1962) observed that this absorption was characteristic of all such saturated dicyano ester. They also found that while this absorption was there in ethanol, it was significantly absent in heptane or acetonitrile, and the intensity of the band increased with the dilution of the ethanolic solution. They suggested that the anomalous absorption maximum in such compounds might be due to the enolization of the dicyanoester, represented by (148). But, we considered (Banerjee 1970) that while such solvent behaviour was exactly the reverse of

that observed in the case of open-chain β -diketones/ β -keto esters, which exist as chelates in non-polar solvents, it is characteristic of cyclic β -diketones (Eistart and Reiss 1954) where chelation is not possible, and, therefore, the other mode of enolization (149) giving rise to the linear ketenimine group, where also the chelation is not possible, is taking place. In order to prove the mode of enolization, we examined the UV spectra of a number of compounds of the types (150, 151, and 152) and that of 153, and it was found that tricyano compounds (150) showed maximum at 231, the others, where enolization of the type (148) was only possible, were transparent. Examination of the IR spectra of the dicyano and tricyano compounds revealed that while in chloroform solution peaks only at 1735 and 2270 cm^{-1} for the C=O (ester) and C $\equiv$ N respectively were observed, in chloroform-methanol solution there were two peaks at 1745 and 1720 cm^{-1} and another extra peak at 2000–2100 cm^{-1} , besides the cyano peak. In the ketenimine structure (149), the ester carbonyl is conjugated and the first two peaks clearly indicated the presence of both the saturated and unsaturated ester carbonyls. Regarding the latter extra peak, we later found (Banerjee *et al* 1974) that it is present in all cyano compounds and might have been due to the hydrogen bonding between the proton donor alcohol and the π -electrons of the cyano group.

6.5 Conformational studies of 8-isotestosterone, 8-iso-10-isotestosterone and 8-iso-10-iso-19-nortestosterone by x-ray crystallography

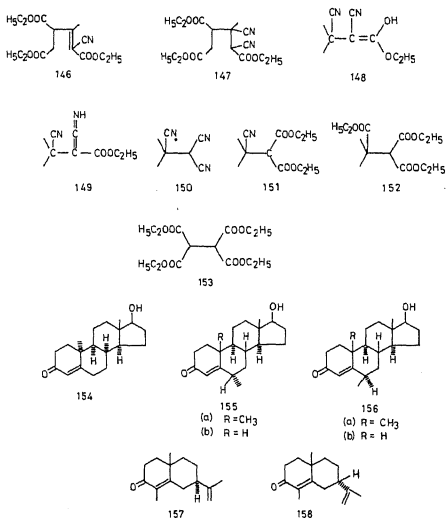
Earlier a total synthesis (Banerjee *et al* 1960, 1964) of 8-isotestosterone (91), which was obtained by Djerassi *et al* (1957) from diosgenin, has been described. Interest centred around this molecule because of its physiological activity, its ORD curve being different from that of testosterone (87,a), a boat shape of the B-ring, suggested by Djerassi and also by us from the mode of formation of the A-ring in our synthesis. The comparison of the solution IR spectra of our *dl*-product and of Djerassi's compound, taken on different machines, was also not entirely satisfactory. X-ray crystallographic investigation of our synthetic compound was undertaken with the view to confirming its structure and configuration and, if possible, finding a solution to the divergence of the ORD curve of Djerassi's compound from that of testosterone. We also studied (Bhadbhade *et al* unpublished) *d*-8-iso-10-iso-19-nortestosterone (96), prepared by us (Banerjee *et al* 1968, 1969; Velluz *et al* 1963; Bucourt *et al* 1968, 1969) and *d*-8-iso-10-isotestosterone (154), a sample supplied by Dr P Westerhof, by x-ray crystallography to find the possibility of establishing a structure-activity relationship. These studies thoroughly confirmed the assigned structure and configuration (91). 8-Iso-testosterone (91), as was observed (Roberts *et al* 1973, 1978) in the case of testosterone (87,a), exists as two crystallographically-independent molecules, the conformation of the B-ring in both corresponding to the twist form, but, differing significantly from one another. The A/B, B/C, C/D ring junctions are *quasi-trans*, *cis* and *trans* respectively. It is noteworthy that whereas testosterone (87,a) is essentially a flat molecule, 8-isotestosterone (91) has folded structure. We could find a solution (Chakrabarti *et al* 1981) for the difference in the ORD curves of optically active 8-isotestosterone and testosterone from the following considerations. It was reported by Djerassi and coworkers (Djerassi 1950; Djerassi *et al* 1958) that while the ORD curve of the equatorially substituted 6- α -methyl-testosterone (155,a) was essentially the same as that of testosterone (87,a), there was a profound change in the ORD curve with the removal of one of the axially substituted 6 β -methyl

testosterone (91). That this was due to the non-bonded interaction between the axial methyls at C-6 and C-10 resulting in conformational distortion was proved by the observation (Villotti *et al* 1959) that the removal of the methyls at C-10 of 155,a and 156,a led to 6 α - and 6 β -methyl-19-nortestosterone (155,b and 156,b) having ORD curves almost identical with those of C-6-unsubstituted Δ^4 -3-keto steroids. It may be pointed out that the possibility of serious non-bonded interaction exists between the methyl at C-10 and β -substituents at C-6, C-8 and C-11, depending upon the distances. It was found that the distances from C-19 to C-6, C-8 and C-14 are essentially the same in both the isomers, whereas distances between C-19 and C-11 in 8-isotestosterone (2.844 and 2.899 Å) are significantly shorter than those in testosterone (3.722 and 3.412 Å, Roberts *et al* 1973). This led to comparatively a much greater non-bonded interaction involving the C-10 methyl of 8-isotestosterone and has been responsible for the change in its ORD curve similar to what happened in the case of 6 β -methyltestosterone (156,a). This also finds a solution to the observed difference of ORD curves of the optically active 8-isotestosterone (91) and 8-iso-19-nortestosterone (95), because of the absence of non-bonded interaction (Villotti *et al* 1959) in the latter by the removal of the C-10 methyl. As mentioned earlier, 8-isotestosterone exhibited 40% of the androgenic activity of testosterone. But, 8-iso-10-isotestosterone (154) and 8-iso-10-iso-19-nortestosterone



a more important role in the androgenic receptor binding than the detailed electronic structure of the A-ring. Whereas, Busetta *et al* (1977) suggested that the activity of the androgenic steroids depend on the orientation of the hydroxyl and the carbonyl groups. It may be seen (Bhadbhade *et al* unpublished) from figure 1 which shows the view of both the molecules of testosterone (87,a) and 8-isotestosterone (91), 8-iso-10-isotestosterone (154) and 8-iso-10-iso-19-nortestosterone (96), looking down C-12 . . . C-14, that the molecules of 91, 154, and 96 are folded at the B/C ring junction in contrast to the flatness of testosterone (87,a) and the buckling is more prominent in 154 and 96. Further, while the relative orientation of the hydroxyl and the carbonyl groups in 91 is similar to that of testosterone, the same in 154 and 96 are quite different from the other two, being situated on the same side resulting in shorter distance between the two groups compared to the other two compounds (87,a and 91) which have the 17-OH and 3-CO on the opposite sides. These perhaps explain the 40% activity in 91 and the absence of activity in 154 and 96. Currently, we are investigating by x-ray crystallography α -cyperone (157) β -cyperone (158) showing (Djerassi 1956) ORD difference similar to that of 87,a and 91.

CHART XIV



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Structures of some unusual types of organic compounds

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Abstract. Structures of a variety of compounds isolated in reactions and elucidated with the help of spectral (UV, IR, NMR and mass) data, have been discussed. In a few cases, the assigned structures were confirmed by x-ray crystal structure analysis.

Keywords. Steroids; seco-steroids; abietic acid; mass spectrum; infrared; acylation; alkylation; isoxazole; cyclisation; oxidation; halogenation; x-ray crystallography.

1. Introduction

Chemistry of natural products including structure determination has attracted wide attention. With the innumerable number of new classes of compounds isolated and identified, it is hard to look for new classes of compounds. Further, competition is quite keen. However, quite often, reactions in the laboratory produce minor amount of byproducts or sometimes major amount of unexpected products. Isolation and determination of structures of these products are quite challenging and the nature of the byproducts, quite often, throws much light on the mechanism of the reaction. Also, elucidation of the structures of these products helps in developing new chemistry. It is thus rewarding to look carefully into minor products obtained in organic reactions. With the modern techniques of separation (TLC, HPLC and GLC) available, it is not that difficult to separate and purify organic compounds. In the following pages, the structures of a variety of compounds are discussed, some simple and others complex (isolated in reactions) elucidated with the help of spectral data. In a few cases, the structures proposed have been confirmed by x-ray crystal structure analysis.

2. Discussion

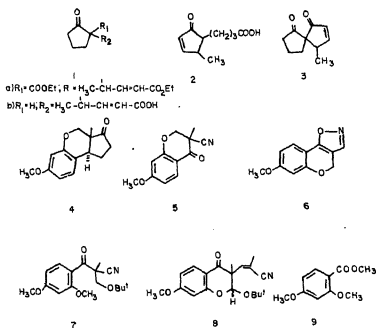
2.1 Rearrangement during acid hydrolysis

As a model study for the introduction of the bile acid side chain by the condensation of ethyl 4-bromo-2-pentenoate with a suitable β -keto ester derivative followed by hydrolysis and decarboxylation, we had condensed the above unsaturated bromo ester with 2-carbethoxycyclopentanone to obtain the substituted keto ester (**1a**). Herz (1956) had shown earlier that such condensation products, after reduction, yielded rearrangement products on treatment with conc hydrochloric acid. When the condensation product (**1a**) was treated under Herz's condition, a mixture of the normal acid (**1b**) and the rearranged acid (**2**) was obtained. The structure of the rearranged acid was evident from its UV spectrum. When the condensation product was treated with a more dilute acid *viz* 10% sulphuric acid, the normal product could be obtained in 93% yield. The above results could be explained on the basis of formation of a spirodiketone (**3**) in the

presence of strong acids. The spirodiketone (3) could open either way to give rise to the mixture of rearranged (2) and normal (1b) products.

2.2 Products of isomerization of isoxazole

In connection with the synthesis of 11-oxasteroid analogs, a stereospecific synthesis of a key intermediate (4) using the well-known benzhydrindane approach for the construction of *transfused* C/D rings (Johnson *et al* 1947; Banerjee *et al* 1956) was required. The starting material for this synthesis was the cyanomethyl chromanone (5). We anticipated that this could be easily synthesised from the corresponding isoxazole (6) following Johnson's procedure for the carbocyclic analog (Johnson *et al* 1945). When the isoxazole (6) was treated with potassium-*t*-butoxide in *t*-butanol at 75–80° (10 min) followed by treatment with methyl iodide and refluxing for 10 hr, a number of products were formed. The required cyanomethyl ketone (5) was formed in small amounts. The mixture of products could be separated by careful column chromatography followed by thin layer chromatography. A detailed study of the UV, IR, NMR and mass spectra of these compounds suggested their structures to be 7–11. The formation of these products was explained through the base-catalysed ring opening of the chroman ring after isomerization of the isoxazole (Kasturi and Damodaran 1966; Kasturi *et al* 1970a, b, 1975, 1976). The occurrence of sharp signals at δ 1.1 (4.5H), 1.28 (4.5H), 3.7 (1H) and 4.24 (1H) in the NMR spectrum of 11, which is apparently anomalous, is best explained by assuming it to be a mixture of fortuitously equal amounts of geometrical isomers (11a and 11b). The isomers could not, however, be separated. The peaks at δ 1.1 and 3.7 were assigned respectively to the *t*-butyl and oxymethylene groups shielded by



the aromatic ring in the isomer 11a and those at δ 1.28 and 4.24 to the *t*-butyl and oxymethylene groups in the isomer 8b (Kasturi *et al* 1970). By employing weaker bases like NaOEt, NaOMe or NaOCH(CH₃)₂ the keto nitrile (5) was obtained as the major product (Kasturi *et al* 1976). Further, the structure of one of the products (10), was confirmed by an alternate synthesis from the chromano-chromanone (12) obtained as a byproduct in the formylation of 7-methoxychroman-4-one as indicated in scheme 1 (Kasturi *et al* 1970).

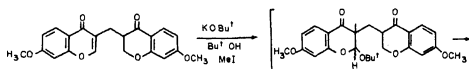
2.3 Dehydrogenation studies with methyl abietate

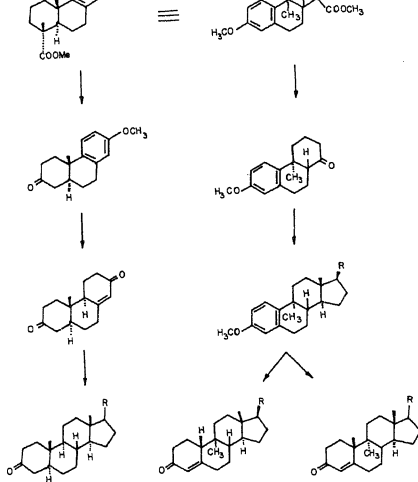
Methyl 13-hydroxydeisopropyldehydroabietate (13a) prepared earlier by Wenkert *et al* (1961), Burgstahler and Worden (1961) and Cambie and Franich (1971) from abietic acid in a low overall yield involving a large number of steps, is a key intermediate (scheme 2a) for the synthesis of natural as well as modified steroids (Banerjee and Kasturi 1971). We could synthesise the same (13a) by a novel shorter route in a considerably more improved yield utilising an adduct obtained in the reaction of methyl abietate with tetrachloro-*o*-benzoquinone (*o*-chloranil) (Kasturi *et al* 1966).

With a view to bring about the dehydrogenation of methyl abietate to methyl dehydroabietate (13b), the reaction of methyl abietate with 1 mole of *O*-chloranil in benzene was carried out. Instead of the expected product, a solid ester in 41 % yield was obtained. This on hydrolysis with 10% butanolic potassium hydroxide gave the corresponding acid (14b). Diazomethane esterification of the acid (14b) gave back the original ester (14a). Hydrogenation of the solid ester gave a tetrahydro derivative. The presence of 4 chlorine atoms (isotopic cluster in mass spectrum) and the UV absorption maximum at 236 nm characteristic of abieta-diene system (Rao 1961), indicated that this could be an adduct. A detailed study of the NMR spectrum of the solid confirmed the structure as 14a, which could also be converted into the corresponding dehydroabietate derivative (15) by treatment with *O*-chloranil. The formation of the adduct (14a) could be rationalized by a dehydrogenation addition mechanism (Banerjee *et al* 1968). The increase in the yield of the adduct to 80 % by using 2 moles of the quinone for one mole of methyl abietate lends support to it. Further, similar treatment of limonene gave an addition compound (16) which was also obtained from *p*-cymene and this seems to be a general method for functionalisation of an isopropyl group on an aromatic ring or an ethylenic linkage.

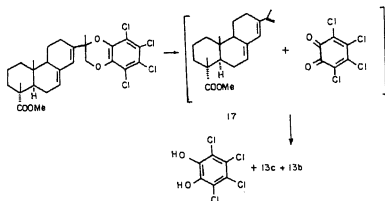
In view of the formation of the adduct in good yield, attempts were made to utilise this for the synthesis of the key intermediate (13a). A perusal of the mass spectrum of

Scheme 1





Scheme 2b

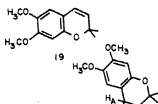
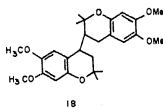
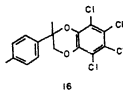
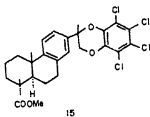
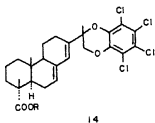
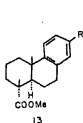


the adduct (13a) indicated that the retro-Diels-Alder fragment at m/z 314 was the base peak. This led us to study the thermal decomposition of the adduct (13a) which yielded a mixture of the styrene derivative (13c) and methyl dehydroabietate (13b). A probable mechanism of formation of the pyrolysis product consists (scheme 2b) of the reversal of the adduct formation at the high temperature followed by dehydrogenation of the triene (17) with the generated quinone to give the styrene (13c) and the hydroquinone

and partly by the rearrangement of **17** to give methyl dehydro-abietate (**13b**) (Banerjee *et al* 1968).

2.4 Dimer of ageratochromene

We have reported (Kasturi and Manithomas 1967) the isolation of a dimer (**18**) of ageratochromene (**19**) from the essential oil of *Ageratum conyzoides*. In order to prove its structure, the same compound (**18**) was synthesised by dimerisation of ageratochromene (**19**) with methanolic hydrochloric acid or mixture of acetic-sulfuric acid. Another solid obtained in this reaction was also shown (spectral data) to be a dimer of ageratochromene (Kasturi *et al* 1973). The NMR spectrum showed the presence of only three aromatic protons (sharp singlets at δ 6.25, 6.37 and 7.3) and no olefinic protons. The 60 and 100 MHz spectra of this solid showed a doublet at δ 4.45 (1H) with the same separation (7 Hz) in each case; this must arise from a single nucleus, probably a doubly benzylic proton. The separation of the three singlets (12H) at δ 3.78, 3.81 and 3.90 in the 60 and 100 MHz spectra are in the ratio 6:10; hence, these signals must be due to four methoxy groups. The four methyl signals at δ 1.27, 1.35, 1.43 and 1.5 are distinct and show no coupling to any other protons; their separations at 60 and 100 MHz are in the expected ratio of 6:10. These methyl groups must arise from two gem-dimethyl groups.



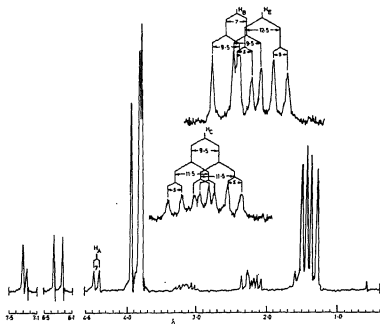


Figure 1. PMR spectrum of dimer (22)

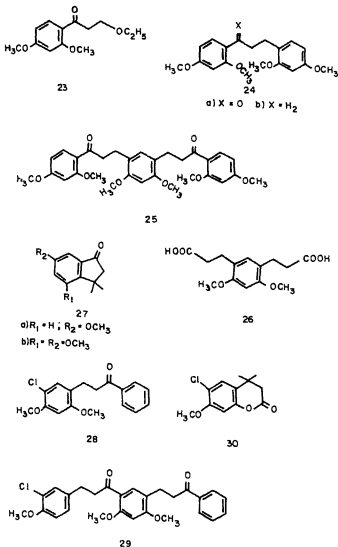
On the basis of the mass spectral fragments m/z 287 (20) and 231 (21), and on the basis of spin decoupling experiments (figure 1), a cyclopentabenzopyran structure (22) was proposed (Kasturi *et al* 1973). The splitting pattern of the protons H_A , H_B , H_C , H_D and H_E in (22) was similar to that in isolapachenole (23) (Cotterill *et al* 1968). A suitable mechanism to explain the formation of this dimer (22) has been proposed.

2.5 Reactions of 1,3-dimethoxybenzene derivatives

Acylation of 1,3-dimethoxybenzene with 3-ethoxypropionic acid using polyphosphoric acid at 40° for 3–5 minutes was expected to give 23. Compound 23 was not formed in the reaction. However, two ketonic substances designated A and B were isolated. Ketone A, M^+ m/z 330, showed in NMR 4 methoxy signals [δ 3.81, S(6H) and 3.87, S(6H)] and was assigned structure 24a. The desoxo compound (24b) obtained by hydrogenolysis with diborane was synthesised by an unambiguous method, thus confirming the structure of ketone A.

Ketone B which has an M^+ peak at m/z 522 in its mass spectrum showed $uv \lambda_{\max}$ characteristic of a 2,4-dimethoxy benzoyl chromophore. The presence of a conjugated carbonyl (IR 1660 cm^{-1}) and of six methoxyl groups (δ 3.81, 3.83 and 3.85) and signals at 6.93 (S, 1H) and 7.83 (d, 2H, $J = 9.5\text{ Hz}$) led us to assign the structure 25. The structure was confirmed by an alternate synthesis involving acylation of 1,3-dimethoxybenzene with the diacid (26) in PPA (Kasturi and Damodaran 1969).

Cyclization of 3-(4-methoxyphenyl)-isovaleric acid using phosphorus pentachloride

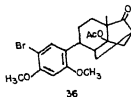
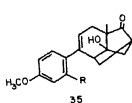
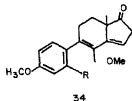
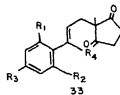
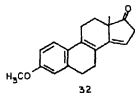
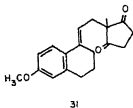


treatment of 3-(2,4-dimethoxyphenyl)-isovaleric acid gave chloro dihydrocoumarin derivative (30). Treatment of dimethoxybenzene derivatives with phosphorous pentachloride appears to be a general method for the preparation of monochloro dimethoxybenzene compounds (Kasturi and Abraham 1973).

2.6 Acid-catalysed cyclizations of *seco*-diones

Acid-catalysed cyclization of *seco*-dione (31) to the corresponding pentaenone (32) is an important step in the Torgov sequence for the total synthesis of steroids (Ananchenko and Torgov 1959, 1963). A variety of reagents have been used with success in this cyclization. We have tried similar cyclizations in a variety of *secodiones*, useful for the synthesis of B-*Seco*- and B-*nor* steroid analogs. (Kasturi *et al* 1982). The unusual types of compounds obtained in the cyclizations will be discussed further.

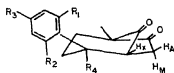
Attempts to effect the cyclodehydration of the *seco*-dione (33a) to the desired B-*seco*-pentaenone (34a) under different conditions failed. However, refluxing a solution of the *seco*-dione (33a) in 20% ethanolic hydrochloric acid for 1 hr gave a mixture of compounds from which a crystalline keto alcohol was isolated. On the basis of spectral



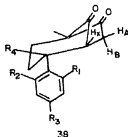
- a) $R_1 = R_3 = \text{OCH}_3$; $R_2 = \text{H}$; $R_4 = \text{C}_2\text{H}_4\text{OCH}_3$
 b) $R_1 = R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{C}_2\text{H}_4\text{OCH}_3$
 c) $R_1 = R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{CH}_3$
 d) $R_1 = R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{CH}_2\text{CH}_3$
 e) $R_1 = R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{Bu}^t$
 f) $R_1 = \text{OCH}_3$; $R_2 = R_3 = \text{H}$; $R_4 = \text{CH}_3$
 g) $R_1 = \text{OCH}_3$; $R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{CH}_3$
 h) $R_1 = \text{OCH}_3$; $R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{CH}_2\text{CH}_3$
 i) $R_1 = \text{OCH}_3$; $R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{vinyl}$
 j) $R_1 = \text{OCH}_3$; $R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{Bu}^t$
 k) $R_1 = \text{CH}_3$; $R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{CH}_3$
 l) $R_1 = R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{H}$
 m) $R_1 = R_2 = \text{OCH}_3$; $R_3 = \text{H}$; $R_4 = \text{CH}_3$

Similarly, cyclization of the monomethoxy secondione (33b) under similar conditions produced the tricyclic keto alcohol (35b). The structure of the compound was evident from its spectral data which were similar to 35a (Kasturi and Ramachandra 1975).

Acid-catalysed cyclization of seco-diones (33a-l) carried out with dry methanolic hydrogen chloride at room temperature resulted in the formation of a mixture of isomeric compounds. These could be separated by thin layer chromatography and were shown by spectral data to be the *exo*- and *endo*-bicyclo[3,2,1]-octane-6,8-diones (37 and 38). These isomeric diones exhibit characteristic line patterns for the oxomethylene and the bridgehead protons in their ^1H NMR spectra. Pattern 'A' (ABX): δ_A, δ_B 2.3–2.8 (m), δ_X 3.1–4 (m); Pattern 'B' (AMX): δ_A 2.4–2.7 (q, $J_{AX} = 8$ Hz, $J_{AM} = 20$ Hz) δ_M 2.8–3 (d, $J_{AM} = 20$ Hz), δ_X 3.3–4.1 (d, $J_{AX} = 8$ Hz). The isomers which exhibited pattern A were assigned the *exo*-2-aryl-*endo*-2-alkyl configuration (37) and those isomers which exhibited pattern B were assigned the *endo*-2-aryl-*exo*-2-alkyl configuration (38). These assignments were based (Kasturi *et al* 1980; Kasturi and Reddy 1981) on the expectation that the aryl group in the *endo* position as in 38 would deshield the *endo*-oxomethylene proton and thus lead to a larger chemical shift difference between *exo*- and *endo*-oxomethylene protons in this isomer. Similar shielding of the *endo*-oxomethylene proton by the *endo*-hydroxyl group in 2-hydroxy-2,5-dimethylbicyclo[3,2,1]octane-6,8-dione has been reported earlier (Hajos and Parish 1974). The spectral features of the bridgehead and the *oxo*-methylene proton signals of 37 and 38 did not agree for the configuration assigned (Kasturi *et al* 1981) and thus necessitated a reinvestigation of the previous assignments. To this end, we carried out the single-crystal x-ray structural analysis of the easily crystallisable isomer of 2-(2-

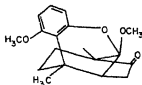


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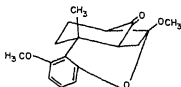


38

- a) $R_1 = R_3 = \text{OCH}_3$; $R_2 = \text{C}_2\text{H}_4\text{OCH}_3$
 b) $R_1 = R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{C}_2\text{H}_4\text{OCH}_3$
 c) $R_1 = R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{CH}_3$
 d) $R_1 = R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{CH}_2\text{CH}_3$
 e) $R_1 = R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{Bu}^t$
 f) $R_1 = \text{OCH}_3$; $R_2 = R_3 = \text{H}$; $R_4 = \text{CH}_3$
 g) $R_1 = \text{OCH}_3$; $R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{CH}_3$
 h) $R_1 = R_3 = \text{OCH}_3$; $R_2 = \text{H}$; $R_4 = \text{CH}_2\text{CH}_3$
 i) $R_1 = R_3 = \text{OCH}_3$; $R_2 = \text{H}$; $R_4 = \text{vinyl}$
 j) $R_1 = R_3 = \text{OCH}_3$; $R_2 = \text{H}$; $R_4 = \text{Bu}^t$
 k) $R_1 = R_4 = \text{CH}_3$; $R_2 = \text{H}$; $R_3 = \text{OCH}_3$
 l) $R_1 = R_2 = \text{H}$; $R_3 = \text{OCH}_3$; $R_4 = \text{H}$
 m) $R_1 = R_2 = \text{OCH}_3$; $R_3 = \text{H}$; $R_4 = \text{CH}_3$



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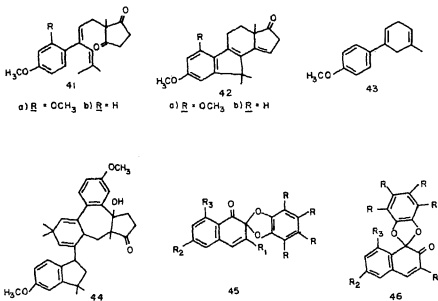


40

exo-2-methyl-*endo*-2-(2-methoxyphenyl) configuration (38f) contrary to the assigned configuration (37f). Consequently, all the previous assignments had to be revised; the isomers which exhibited pattern A are now assigned the *endo*-2-aryl-*exo*-2-alkyl configuration and *vice-versa* (Kasturi *et al* 1981). ^1H and ^{13}C NMR of several bicyclo[3,2,1]octane diones have been discussed (Kasturi *et al* 1982).

Reaction of seco-dione (33m) with anhydrous methanolic hydrogenchloride gave 2-*endo*-(2,6-dimethoxyphenyl)-2-*exo*-methyl-5-methyl-bicyclo[3,2,1]octane-6,8-dione (38m) whose structure was confirmed by x-ray crystal structural analysis (Murthy *et al* 1982). No 2-*exo*-(2,6-dimethoxyphenyl)-2-*endo*-methyl bicyclo[3,2,1]octane dione (37m) was formed. Instead, another crystalline solid was isolated which showed a carbonyl frequency at 1740 cm^{-1} and in the NMR, two methyl singlets (δ 1.03 and 1.56), one aliphatic methoxy (3.32) and only one aromatic methoxy (3.79) group. On the basis of spectral data, two structures (39 and 40) were considered. NaBH₄ reduction of the solid gave a mixture of *endo*- and *exo*-alcohols which could be separated. On the basis of the PMR spectra of these alcohols especially the coupling constants, structure (39) was assigned to this solid. Probably, the *exo*-isomer (37m) formed in small quantities gave rise to this compound by a neighbouring group participation to release the excessive buttressing effect (Kasturi *et al* 1982).

Acid-catalysed (CH_2Cl_2 -conc. H_2SO_4) cyclization of the seco-dione (41a) gave the 6-nor-steroid derivative (42a) in fairly good yield. However, cyclization of the 6-methoxy seco-dione (41b) under similar conditions gave very little of the 6-nor steroid derivative (42b), but gave two novel products. The structures of these two products, elucidated using their spectral data (PMR, CMR and mass) have been shown to be the simple cyclohexa-1,4-diene derivative (43) and the complex dibenz-azulene

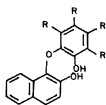


2.7 Oxidation with quinones

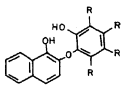
Both 1- and 2-naphthols undergo oxidative coupling with *O*-chloranil to give spirans (Kasturi *et al* 1970). While 1-naphthol gives the spiran (45a) on oxidation, 2-naphthol, unexpectedly affords a mixture of the two spirans (45a and 46a) indicating an unusual oxidative rearrangement. In order to study the generality as well as substituent effects on this novel rearrangement, a number of substituted 1- and 2-naphthols were synthesised (Kasturi and Sivaramakrishnan 1975, 1976) and their oxidative coupling reaction studied (Kasturi and Sivaramakrishnan 1978). It has also been shown that while oxydiphenols (47) undergo normal intramolecular oxidative coupling to give spirans (45) oxydiphenols (47a) undergo rearrangement to give a mixture of the spirans (45 and 46). The presence of chlorine atoms on the benzene ring is not necessary for this oxidative rearrangement as shown by oxidation studies with oxydiphenols (47b) (Kasturi and Ganesh Prasad 1983).

On the basis of this study, it was proposed that the oxidation of 2-naphthol derivatives could go through the formation of spiro-cyclohexadienone intermediate (49) which could open up in either direction to give the α - and β -spirans (45 and 46). The conformation of the phenoxy group, the oxidation potential of the quinone and the substrate (the naphtholic and the phenolic part in the oxydiphenols) along with steric and electronic effects of the substituents could explain the observed results (Kasturi and Ganesh Prasad 1983).

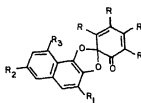
With a view to understand the reaction of *O*-chloranil with a substrate like bis-(2-hydroxy-1-naphthyl) methane (50a), the oxidation was carried out with different proportions of *O*-chloranil. Unexpectedly, spirans (45a & 46a), the dimer of 1,2-naphthoquinone-1-methide (51) along with the intramolecularly coupled product (52) were obtained (Kasturi *et al* 1979). When the reaction of 50a was carried out with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene, an entirely new reaction



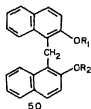
47
a) R = Cl b) R = H



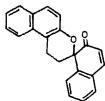
48
a) R = Cl b) R = H



49
(R = Cl or H)



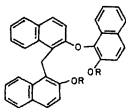
50
a) R₁ = R₂ = H
b) R₁ = H; R₂ = CH₃



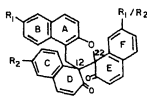
51



52



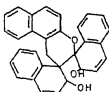
53
a) R = H b) R = CH₃



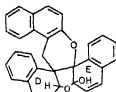
54
a) R₁ = R₂ = H

hydro and the corresponding dimethoxy compounds respectively from a study of their ^1H and ^{13}C NMR spectra were further corroborated by an unambiguous synthesis involving condensation of 50b with 1-bromo-2-methoxy-naphthalene followed by methylation with boron tribromide. On the basis of a detailed study of ^1H and ^{13}C NMR spectra, the unusual dispirodienone structure (54) was assigned to this compound. Results obtained from x-ray crystal structure analysis are in full agreement with this structure. It has been found that the $\text{C}_{12}\text{--C}_{22}$ bond is unusually long (1.616 Å) in this compound (54). A small amount of the *trans* product of 54 was also obtained in this oxidation (Kasturi *et al* 1984). Using this reaction, a series of bispironaphthalenones (4) (with different substituents (R_1 & R_2)) have been synthesised and a suitable mechanism suggested for its formation (Kasturi *et al* 1984).

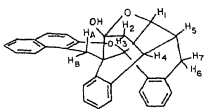
With a view to preparing the biallylic alcohol (55) required for some studies of intramolecular (2 + 2) photocycloadditions (Kasturi *et al* 1981), the bispironaphthalenone (54) was reduced with sodium borohydride in THF. The biallylic alcohol (55) was obtained in only 15% yield. The major products of this reduction were the acetal (56) and the novel intramolecularly c-c coupled acetal (57). When the reduction was carried out with NaBH_4 in the presence of NaOH in aqueous THF, 56 was obtained with traces of 55 and 57. However, reduction in MeOH-THF containing NaOH gave the novel ethoxy c-c coupled acetal (58a) in good yield. Similarly, the ethoxy (58b) and the propoxy (58c) c-c coupled acetals were also prepared. The structures of all these compounds were established by ^1H and ^{13}C NMR spectral studies. The off-resonance coupled ^{13}C NMR spectra of 57 shows three triplets and four doublets < 90 ppm, clearly indicative of intramolecular c-c coupling between the D & E rings. The



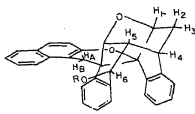
55



56



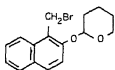
57



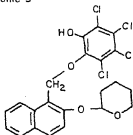
58

a) R = Me b) R = Et c) R = Prⁱ

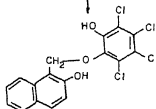
Scheme 3



59



60a



60

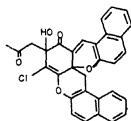
benzylic carbon atoms was established by their ^1H NMR spectra. Of the two alternative resulting structures, that with coupling between the D-ring benzylic carbon atom and the E-ring non-benzylic carbon atom was assigned to **57** on the basis of the OH resonances. There are significant differences in the ^1H NMR spectra of **57** and **58** in particular, the 1-H (*d* in **57**; *m* in **58**) and 2,3-H resonances (*dd* in **57**; AB '*q*' in **58**). The variation on the OH resonance position with the alkoxy group in **58** (R = CH₃, δ 5.33; R = Et, 5.43; R = Prⁱ, 5.50; cf **57**, 2.67) indicates that the hydroxy group is on the same side as the alkoxy group and probably hydrogen bonded to it (Kasturi and Raju 1982).

In connection with the oxidation studies, we needed the oxydiphenol (**60**). The synthesis of **60** was planned as indicated in scheme 3. The starting material (**59**) was prepared by NBS bromination of the pyranyl ether of 1-methyl-2-naphthol. However, when the condensation of the bromo compound (**59**) with tetrachlorocatechol was carried out in refluxing acetone in the presence of anhydrous potassium carbonate, the

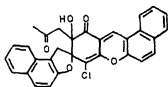
required compound (60a) was not formed. Instead, two isomeric compounds ($M^+ 508$) A and B and the dimer of 1,2-naphthoquinone-1-methide (51) were obtained. The presence of one chlorine atom was noticed in the mass spectrum of the isomeric compounds. The $^1\text{H NMR}$ spectra of the isomeric compounds exhibited two AB quartets, an OH signal (sharp in one case) and signals in the aromatic region. On the basis of the spectral data, 3 alternative structures (61, 62, 63) were considered, but structure (62) was considered more probable for compounds A & B. By a study of the $^{13}\text{C NMR}$ of these compounds in the presence of TAI reagent (Bose and Srinivasan 1975), it is now concluded that the two compounds A & B are diastereomers having structures (64a) and (65a). When the reaction was carried out with tetrabromocatechol instead of trichlorocatechol the corresponding isomeric monobromo compounds (64b and 65b) were isolated. Further confirmation of the structures by x-ray crystal structure studies is in progress (Kasturi *et al* 1983).

Oxidation of Abel's ketone (52a) with DDQ in dry benzene resulted in the formation of two products designated A and B, which show carbonyl absorption frequencies at 1628 and 1760 cm^{-1} respectively. Mass spectra ($M^+ m/z 296$) show that the two compounds are isomeric and are dehydrogenation products of 52. In $^1\text{H NMR}$ spectra, all the proton signals are in the aromatic region. On the basis of spectral analysis, a furanotropone structure (66) was assigned for compound A. The spectral properties are comparable to those of an isomeric furanotropone (67) reported in the literature (Chatterjee *et al* 1978). Further, the spectral properties of compound A and its dihydroderivative (68a) are similar to those of compounds (66b and 68b) reported by Dean and coworkers (Dean *et al* 1964). The tropone structure (66a) explains the presence of two deshielded proton doublets at $\delta 8.64$ and 9.6 in its NMR spectrum. X-ray crystal structure analysis of compound A confirmed its structure as 66a (Kasturi *et al* 1984).

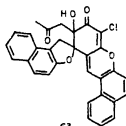
The high carbonyl frequency 1760 cm^{-1} of compound B implied the presence of a ketone moiety. On the basis of available spectral data of compound B and its transformation products (69 and 70), a tentative benzfulvene type of structure 71 has been assigned. Further work is in progress to confirm this structure.



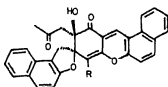
61



62

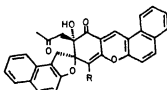


63



64

a) R = Cl b) R = Br



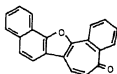
65

a) R = Cl b) R = Br

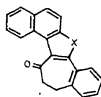


66

a) X = O b) X = NH

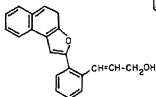


67

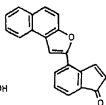


68

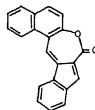
a) X = O b) X = NH



69



70



71

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A facile synthetic route to complex polycyclic natural products through intramolecular alkylation with α -diazomethyl ketones

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Abstract. Some applications of the intramolecular alkylation of α -diazomethyl ketones through metal-catalysed addition and insertion reactions, and acid-catalysed olefinic and aryl participations, towards the synthesis of a variety of complex polycyclic natural products have been briefly reviewed with special emphasis on the results reported from the authors' laboratories. The possible mechanisms of the transition metal catalysed carbon-carbon bond forming reactions of carbenoids have been briefly discussed in the light of the recent literature.

Keywords. α -diazomethyl ketones; intramolecular alkylation; α -ketocarbenoids; metal-catalysed reactions; acid-catalysed reaction; polycyclic synthesis.

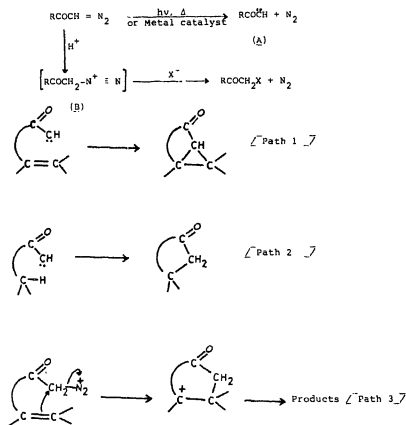
1. Introduction

The intramolecular reactions of α -diazocarbonyl compounds have received considerable attention as they lead to the construction of a variety of complex carbocyclic framework not easily accessible by conventional methodologies. The wide application of this intramolecular process is found in the total syntheses of gibberellins (Mander 1983), phyllocladene (Tahara *et al* 1973), sirenin (Bhalerao *et al* 1970 and references therein), α -chamigrene (White *et al* 1974) and sabinene (Vig *et al* 1969) as well as the synthesis of theoretically interesting compounds such as bullvalene (Doering *et al* 1967), twistane (Tichy 1972) and bridged annulenes (Vogel *et al* 1970; Vogel and Reel 1972).

Two principal reactive intermediates are available from α -diazocarbonyl compounds: α -ketocarbenes (or α -ketocarbenoids) (A) and α -diazonium ketones (B) (scheme 1). The ketocarbenes, generated by decomposition of α -diazoketones by thermal, photochemical or metal catalysis process, can undergo two major classes of reactions: (a) addition to either C=C double bond in a second molecule (intermolecular addition) or to an appropriately situated olefinic group in the same molecule leading to a cyclisation reaction (path 1), (b) insertion into C-H bond of a second molecule or within the same molecule (path 2) (scheme 1). The third major class of reaction undergone by α -diazoketone is through α -diazonium ketone (B) which undergoes nucleophilic substitution with displacement of nitrogen (scheme 1). In an intramolecular reaction, an appropriately situated olefin or aromatic ring can act as the nucleophile leading to a cyclisation reaction (path 3) of great synthetic utility. A detailed discussion of all these reactions is beyond the scope of this review.

A comprehensive account of these three aspects of the α -diazoketone reactions was

Scheme - I



given by Burke and Grieco (1979). The acid catalysed reactions of α -diazoketones have been recently reviewed by Ghatak (1981) and Smith *et al* (1981). The present report includes the recent work in this area with special emphasis on the contributions made from authors' laboratories.

2. α -ketocarbenes or α -ketocarbenoids

Photochemical, catalytic or thermal conditions are employed for generation of ketocarbenes from α -diazoketones. Of these, catalytic (homogeneous or heterogeneous) conditions are most commonly used in synthetic organic chemistry. Until recently, all the reported catalytic decompositions were carried out under heterogeneous or homogeneous conditions with a variety of copper catalysts (Burke and Grieco 1979). Recently a few efficient and selective catalysts, for example copper(I) trifluoromethylsulphonate [CuTf] (Salomon and Kochi 1973) and some group 8 metals such as rhodium(II) (Anciaux *et al* 1980; Dowd *et al* 1982) and palladium(II) (Anciaux *et al* 1980; Smeets *et al* 1980) have been introduced for intermolecular cyclopropanation reactions of olefins with diazocompounds. Another significant development is the highly enantio-selective synthesis of cyclopropane derivatives involving carbenoid reactions between olefins and diazoalkanes catalysed by bis[(-)-

1981) reported, for the first time, that *bis*[2,4-pentanedionato]nickel(II) [Ni(acac)₂] acts as a highly efficient homogeneous catalyst in these reactions. Only a single unsuccessful attempt at cyclopropanation using a nickel catalyst, nickelocene, has been recorded (Werner and Richards 1968).

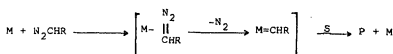
1 Mechanism

From extensive mechanistic studies based upon mostly the intermolecular cyclopropanation reactions using a variety of homogeneous metal catalysts it has been postulated (Burke and Grieco 1979; Salomon and Kochi 1973; Anciaux *et al* 1980; Wulfman 1976) that two competitive pathways, one originating from the metal-olefin coordination as the key factor and the other, a bimolecular process with metal-carbenoid species attacking uncomplexed olefins are operative in these reactions. The influence of various catalysts on the regioselectivity of cyclopropanations to dienes and trienes was studied in detail by Anciaux *et al* (1980, 1983). From their studies, it is revealed that rhodium catalysts are extremely efficient for cyclopropanations of any kind of alkene, the electron rich double bond being regioselectively cyclopropanated. In contrast, palladium catalysts cyclopropanate the less substituted double bond regioselectively whereas copper catalysts exhibit borderline cases. Based on these results, two fundamental mechanistic pathways have been forwarded: a carbenoid mechanism as shown in scheme 2 and a co-ordination mechanism as shown in scheme 3 (where M = metal complex; S = unsaturated substrate, and P = products). Rhodium(II) carboxylates act exclusively according to scheme 2, while palladium carboxylates probably react according to scheme 3. Copper catalysts generally display a carbenoid (scheme 2) type of behaviour, with the exception of some complexes carrying weak ligands notably copper triflates where the contribution from the mechanism of scheme 3 becomes important.

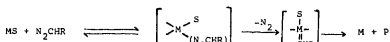
2 Intramolecular ketocarbenoid addition to olefin

The ketocarbene addition to a suitably situated olefin within the same molecule has led to the synthesis of several natural products containing cyclopropyl ring. A brief account of the syntheses of such compounds will be found in the article by Burke and Grieco (1979).

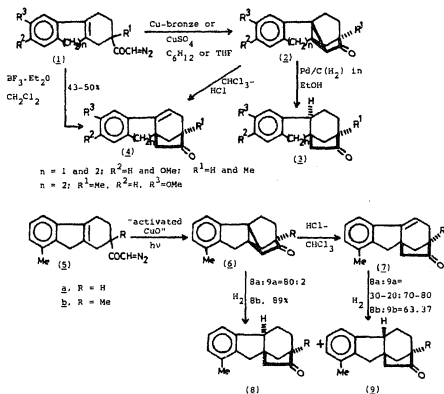
Scheme - II



Scheme - III



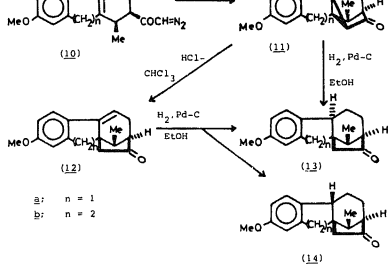
Scheme - IV



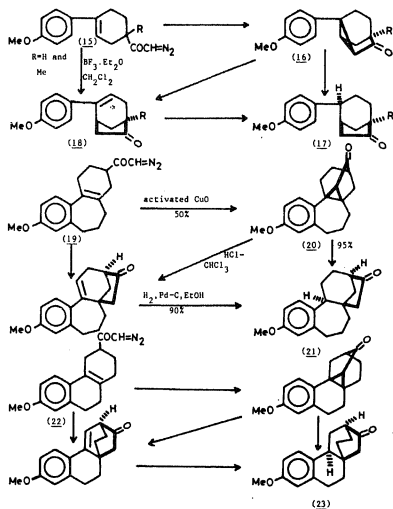
The cyclopropyl ketone resulting from intramolecular cyclisation of an olefinic ketocarbenoid can be cleaved by hydrogenolysis or protonolysis. This strategy has been extensively explored by Dasgupta *et al* (1969), Chakraborty *et al* (1972) and Ghatak and Roy (1981) for the synthesis of a number of bicyclo[3.2.1]octane derivatives (3) and (4) from the diazoketones (1) as depicted in scheme 4. Ghatak and Chakraborty (1979) extended this route for the total syntheses of ($\pm$)gibberone (7b) and ($\pm$)-4-methyl-9 β ,13 α -dihydro-16-oxogibba-1,3,5(10)-triene (9a), two degradation products of gibberellins. It is interesting to note that hydrogenolysis of the cyclopropyl ketones (6) produced exclusively C-9 $\alpha\alpha$ epimer whereas reduction of (7) produced mixture of 9 $\alpha\alpha$ and 9 $\alpha\beta$ epimers leading to the synthesis of C-9 epimeric gibbane synthons.

The conformational effect of a 1 β -methyl substituent on the courses of intramolecular oxocarbenoid addition in the diazoketones (10) and on the stereoselectivities of catalytic hydrogenation of the derived pentacyclic ketones (11a & 11b) and tetracyclic ketones (12a & 12b) was evaluated by Ghatak *et al* (1974). The substituent effect of the aromatic ring in oxocarbenoid addition as well as in the stereoselectivities of catalytic hydrogenation of the cyclopropyl ketone and the gibbane was studied in detail by Ranu *et al* (1982).

This strategy of the synthesis of bicyclo[3.2.1]octane through oxocarbenoid addition reaction has been extended to several other diazoketones *e.g.* (15) by Ghatak *et al* (1976) for the synthesis of intermediates (16–18) towards B-*seco*-gibberellins. A stereospecific synthetic route to a tetracyclic bridged-ring ketone (21) related to the B-homonhylcladane system was developed (Ghatak and Ray 1977) through the

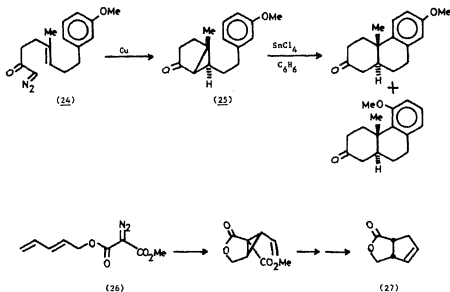


Scheme - VI



A similar strategy was extensively used by Beames and Mander (1969), Beames *et al* (1972) and Mander *et al* (1974) for the construction of bicyclo[3.2.1]octane and bicyclo[2.2.2]octane derivatives.

An interesting application (Stork and Gregson 1969) of the intramolecular olefinic



ketocarbenoid addition reaction is found in Lewis acid-catalysed cleavage of the cyclopropyl ketone (25) derived from (24) with simultaneous participation of a suitably situated olefin or aromatic ring leading to cyclisation (scheme 7).

The intramolecular addition reactions of carbenoids derived from mixed diazomalonate have been applied for the synthesis of prostanoide intermediate (Corey and Fuchs 1972), α -methylene γ -butyrolactones (Ziegler *et al* 1974), spiro lactone and spiro ketone (Clark and Heathcock 1975). Recently, Hudlicky *et al* (1983) applied this strategy to synthesise bicyclic cyclopentene lactones (27) from the diazomalonate (26).

2.3 Intramolecular insertion of α -ketocarbenoids into C-H bond

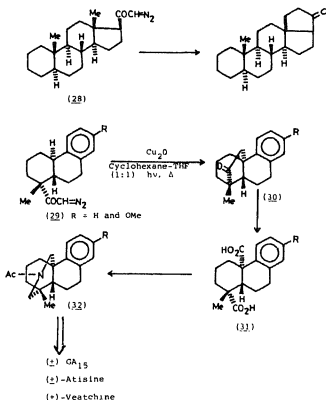
Although relatively less explored, the intramolecular C-H insertion of α -diazocarbonyl compounds has made possible many important and otherwise difficult synthetic transformations. In a geometrically rigid system intramolecular C-H insertion is a highly favoured process.

The first example of intramolecular C-H insertion leading to cyclisation was observed (Greuter *et al* 1958) during decomposition of 21-diazo-5 α -pregnan-20-one (28) in refluxing toluene in the presence of Cu(I) oxide (scheme 8).

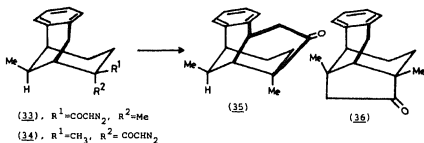
An intramolecular angular alkylation was achieved (Ghatak and Chakrabarty 1972, 1976) through regioselective α -keto carbenoid insertion into tertiary C-H bond of the diazoketones (29) in presence of Cu(II) sulphate or preferentially with Cu(I) oxide. The light induced Ni(acac)₂ catalysed reaction of (29) leads to (30) in excellent yield (Chakraborty *et al* 1984). The bridged cyclopentanones (30) were further transformed to the bridged-acylamines (32) through the respective dicarboxylic acids (31) as illustrated in scheme 8. This sequence represents a highly efficient formal stereospecific total synthesis of dl-atisine, dl-veatchine and gibberellin-A₁₅ (scheme 8). Ghatak *et al* (1976a) extended the C-H insertion reaction to the diastereoisomeric diazoketones (33) and (34) for the syntheses of the bridged-ketones (35) and (36), respectively (scheme 10).

In a systematic study of competitive intramolecular C-H insertion reactions of some substituted cyclohexane derivatives (Chakrabarty *et al* 1975; Chakraborty *et al* 1984), it

Scheme - VIII



Scheme - IX



It was revealed that insertion into $Me-C-H$ bond in (37c) leading to the bridged bicyclo[3.2.1]octanone (39c) is marginally favoured to that $Ph-C-H$ bond resulting in the regioisomeric ketone (38c). Also intramolecular competition in (37a) and (37b) strongly favours insertion into the tertiary benzylic $C-H$ bond leading to mostly (38a) and (38b) rather the secondary ones leading to the respective regioisomers (39a) and (39b). The homogeneous catalyst, $Ni(acac)_2$ is found to be the most effective for these insertions compared to the other catalysts studied such as, Cu_2O , $CuSO_4$, $Pd(acac)_2$ and $Co(acac)_2$.

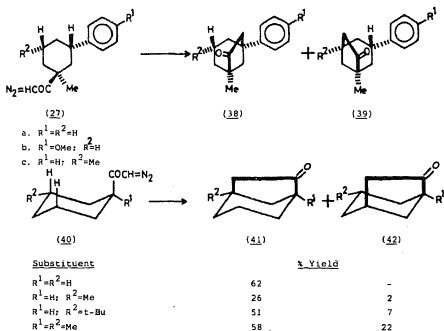
Agosta and Wolff (1975), in their detailed study of the Cu -catalysed decomposition of the diazoketones (40) to the regioisomeric $C-H$ insertion products (41) and (42), pointed out the three following structural effects in controlling the site of $C-H$ insertion

(c) geminal substitution at the carbon bearing the diazocarbonyl group, as revealed from the composition of the products (scheme 10).

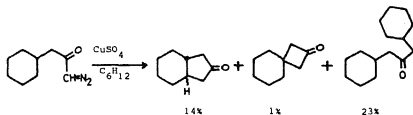
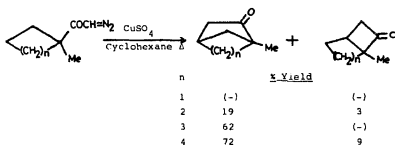
The conformational effect on the regiochemistry in intramolecular C-H insertion reactions was also demonstrated by Wenkert *et al* (1968) (scheme 10). In all the cases studied, formation of a five-membered ring is favoured over the four-membered one.

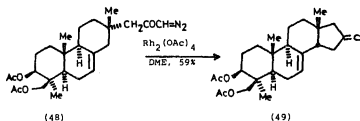
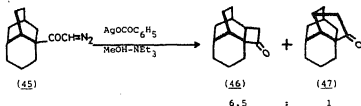
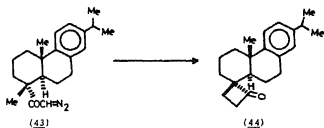
An attempted Wolff rearrangement of the diazoketone (43) by Wenkert *et al* (1975) led to the isolation of C-H insertion product (44) in 22% yield. Similar C-H insertion under Wolff-rearrangement condition of the diazoketone (45) afforded a mixture of (46) and (47); the cyclobutanone (46) being the major product (Takahashi *et al* 1975). Very recently, a diterpene to steroid conversion has been reported (Wenkert *et al* 1982) by an intramolecular C-H ketocarbene insertion reaction of the diazoketone (48), derived from the virescenol B diacetate, to the tetracyclic keto-diacetate (49).

Scheme - X



Scheme - XI





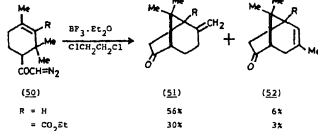
Acid-catalysed carbon-carbon bond formation in α -diazomethyl ketones through π -bond participation

The acid-catalysed cyclisation of diazomethyl ketones through π -participation of suitably situated olefinic bonds or aromatic groups has accumulated a great deal of interest as it provides a good method for carbocyclic ring annulation.

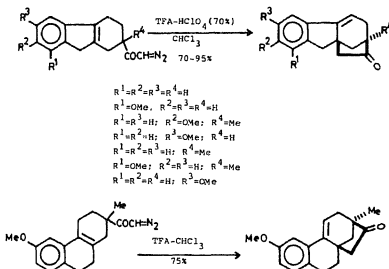
1 Carbon-carbon bond formation from γ,δ -unsaturated α -diazomethyl ketones

A new cyclopentanone annelation reaction of great synthetic potential was developed by several groups for the introduction of a bicyclo[3.2.1]octanone or a bicyclo[2.2.1]heptanone moiety into a variety of carbocyclic systems by the acid-catalysed intramolecular electrophilic cyclisation of γ,δ -unsaturated α -diazomethyl ketones. The first example of acid-catalysed intramolecular olefinic participation was reported by Herman and Stone (1971) in an elegant synthetic approach to the α -patchouline class of sesquiterpene by $\text{BF}_3\text{-Et}_2\text{O}$ catalysed cyclisation of the diazoketones (50) to give the respective double bond isomeric cyclisation products (51) and (52) in moderate to good yields.

During the early seventies several efficient carbon-carbon bond formation reactions involving α -diazomethyl ketones (1) (scheme 4) and (19) (scheme 6) have been studied independently (Chakraborty *et al* 1972; Ghatak *et al* 1976; Ghatak and Ray 1977) for the construction of the tetracyclic intermediates (4) and (20A) (scheme 6) and a number of related compounds incorporating bicyclo[3.2.1]octanone bridged-ring systems towards the total synthesis of several complex diterpenoids. Mander and his co-workers (Mander *et al* 1974; Beames *et al* 1972) have independently developed similar cyclisation reactions of diazoketones leading to the tetracyclic ketones (4, $n = 1$



Scheme - XIV



and 2; $\text{R}^1 = \text{H}$ and Me ; $\text{R}^2 = \text{H}$ and Me) in much improved yield by using HBF_4 in nitromethane.

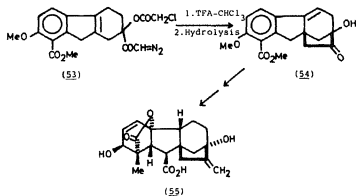
The intramolecular alkylation reactions of unsaturated diazomethyl ketones have been further improved and extended in our laboratories for the preparation of a large number of $\Delta^{9(11)}$ -gibbenes and related compounds as illustrated in scheme 14 (Ghatak and Chakraborti 1979; Ghatak *et al* 1981; Ranu *et al* 1982). The yield of the cyclised products has been substantially improved (70–95%) by using 70% perchloric acid-trifluoroacetic acid as catalyst in chloroform.

Hook *et al* (1980) utilised the tetracyclic ester (54), prepared by cyclisation of the diazoketone (53) in a classic total synthesis of ($\pm$) gibberellic acid (55) (scheme 15).

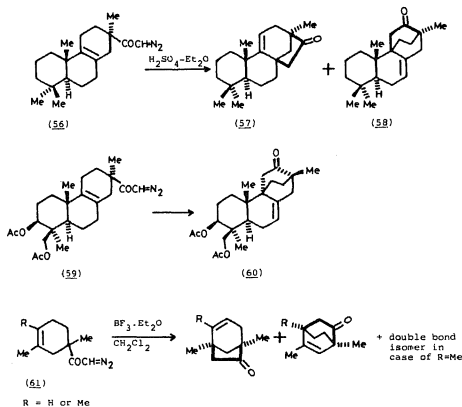
The intramolecular cyclisation was also extended (Ghatak *et al* 1976) for the synthesis of some important intermediates (18) for B-seco gibberellins through the diazomethyl ketones (15) (scheme 6). A similar cyclisation of the diazoketone (22) (Ghatak and Roy 1981) led to a tetracyclic intermediate incorporating the basic bicyclo[2.2.2]octanone skeletal structure of atisine diterpenoids (scheme 6).

In each of the above examples, acid-catalysed cyclisation reaction of $\gamma\delta$ -unsaturated α -diazomethyl ketones produced essentially a single annelated ketone arising through the initial electrophilic attack by the protonated diazo-carbonyl function to the electron rich centre. The absence of such polarisation in the double bond may result in a mixture of the possible regioisomeric cyclised ketones as evidenced (Ceccherelli *et al* 1978) in the cyclisation of (56) to (57) and (58) in a 3:2 ratio (scheme 16). The steric environment

Scheme - XV



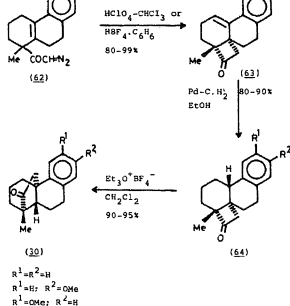
Scheme - XVI



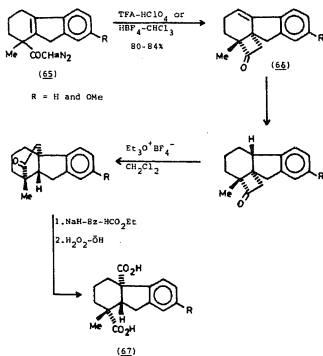
so seems to be important as it reflects in the regiospecific cyclisation of (59) to (60) (scheme 15). Similar lack of regioselectivity in the carbon-carbon bond formation has been observed in some relatively simple substituted monocyclic $\gamma\delta$ -unsaturated diazomethyl ketone (61) in this laboratory (Saha and Chakraborti unpublished work).

2 Acid-catalysed intramolecular C-alkylation in $\beta\gamma$ -unsaturated diazomethyl ketones

The acid-catalysed intramolecular cyclisation of β,γ -unsaturated α -diazomethyl ketones has led (Ghatak and Sanyal 1974) to introduce a highly efficient new synthesis of angularly fused cyclobutanones. The readily available styrenoid cyclobutanones (63) from the respective diazomethyl ketones (62), have been further transformed to the corresponding cyclopentanones (30) (scheme 17) by a remarkable stereospecific



Scheme - XVIII

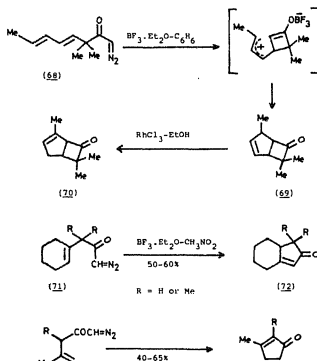


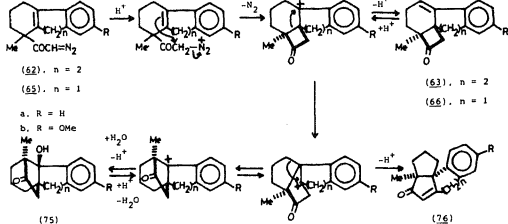
(64). As mentioned earlier, the bridged cyclopentanones (Ghatak *et al* 1978; Ghatak *et al* 1980) are the key intermediates for the total synthesis of atisine, veatchine and gibberellin-A₁₅.

The β,γ -unsaturated α -diazomethyl ketones (65) incorporating a tetrahydrofluorene moiety, also produced the respective styrenoid cyclobutanones (66) which were transformed through a similar sequence of reactions (Ghatak *et al* 1980) to the potential hydrofluorene intermediates (67) towards C₂₀-gibberellins (scheme 17).

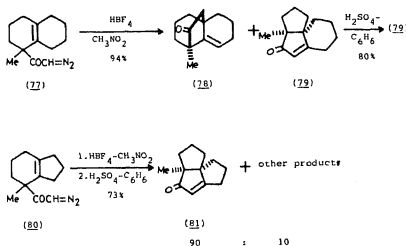
This cyclobutanone annelation was utilised by Ceccherelli *et al* (1980) for the preparation of two 4,4-dimethyl-D-norsteroids. Hudlicky and Kutchan (1980) applied this method on the diazomethyl ketone (68) to the respective cyclobutanone (69) and finally to filifolone (70) (scheme 19). Smith *et al* (1975) and Smith and Dieter (1977) developed the acid-catalysed alkylation method to a few relatively flexible β,γ -unsaturated α -diazomethyl ketones *e.g.* (71) and (73) leading to the corresponding cyclopentenones (72) and (74) (scheme 19) as sole products. Extensive studies on the related cyclopentenone annulation reaction and its extension were reported by Smith *et al* (1981). After considerable experimentation, Ghatak *et al* (1981), discovered that it is not the structure of the substrate alone which controls the nature of the products in the acid-catalysed reactions of the β,γ -unsaturated diazoketones such as (62) and (65) but that the choice of the acid catalyst and solvent is also critical. For example, the reactions of the diazoketones (62) and (65) in weakly polar solvents such as benzene, chloroform or methylene chloride in the presence of strong protic acids namely aq. HClO_4 (70%), aq. HBF_4 (48%), CF_3COOH or H_2SO_4 (98%) gave the respective unsaturated cyclobutanones (63) and (66) in good to excellent yields. In contrast, when the diazoketones (62) and (65) were subjected to cyclisations (Ghatak *et al* 1981; Satyanarayana *et al* 1982; Roy *et al* 1982) with aq. HBF_4 (48%) or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in strongly polar solvent nitromethane, the respective rearranged bridged hydroxycyclopentenones (75, $n = 2$) were predominating product (*ca* 90%) (scheme 20). The hydroxycyclopentanones (75, $n = 2$) underwent facile rearrangement with *p*-TsOH or iodine in boiling benzene to afford the respective rearranged cyclopentenones (76, $n = 2$). In contrast, the hydrofluorene analogues (75, $n = 1$) under similar conditions did not produce the rearranged cyclopentenones (76, $n = 1$). These compounds, however, have been obtained in excellent yields (Satyanarayana *et al* 1981) by direct cyclisations of the diazoketones (62, $n = 1$) with *p*-TsOH in boiling benzene. The mechanistic pathways

Scheme - XIX





Scheme - XXI



for the formation of different products from the diazomethyl ketones (62) and (65) have been rationalised as depicted in scheme 20.

The alkylation rearrangement reaction has also been extended (Satyanarayana *et al* 1981) to the bicyclic diazoketone (77) leading to the bridged ketone (78) and the rearranged cyclopentenone (79) (scheme 20) in excellent yields. This mixture undergoes facile acid-catalysed rearrangement to (79). The lower homologous diazomethyl ketone (80) undergoes cyclisation-rearrangement to afford the angularly fused cyclopentenone (81) along with other minor products. This sequence appears extremely attractive for the synthesis of complex polycyclopentanoid sesqui- and sesterterpenes. A similar alkylation-rearrangement of a diazomethyl ketone has been exploited previously (Takano *et al* 1978) for the synthesis of an intermediate towards aspidosperma alkaloids.

3.3 Intramolecular alkylation of diazoketones through aryl participation

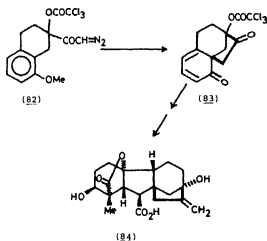
The elegant studies of Mander (1983) have elaborated the aryl participations in protonated diazomethyl carbonyl alkylations as a viable method for bridged- and spiro-ring annelations, leading to an elegant synthesis (Lombardo *et al* 1980) of (±)-

berellin-A₁ (84) as depicted in scheme 22, starting from the diazoketone (82) through the aryl participated product (83).

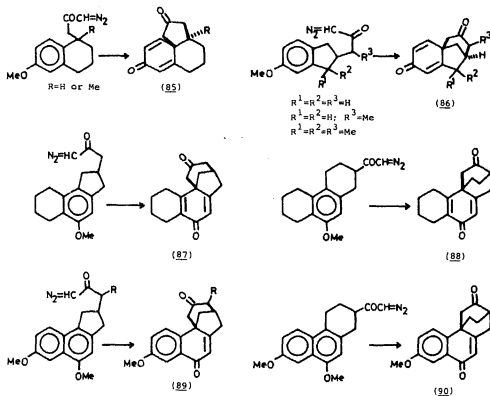
Spiroannulation reactions have been extended by Bhattacharya and Sen (1979) for the synthesis of spirocyclobutanone and a few spirocyclopentanones.

Ring annulation by aryl participation has been successfully utilised by Sanyal *et al* (1978) and Mukherjee *et al* in these laboratories, for preparation of the spiro- and bridged-ketones (85), (86) and a number of related compounds as key intermediates towards the synthesis of sester- and sesquiterpenoids. Several tetracyclic skeletons *e.g.* (87), (88), (89), and (90) related to a number of diterpenes have been prepared in these laboratories (Maity *et al* 1982, 1983; Maity and Mukherjee 1984a, b) Basu *et al* 1981; Basu and Mukherjee 1984) through aryl participation (scheme 23).

Scheme - XXII



Scheme - XXIII



4. Conclusions

The intramolecular alkylation of diazomethyl ketones provides a facile synthetic entry to a variety of complex polycyclic natural products incorporating functionalised quaternary carbon residues. With appropriate selection of the substrates and reaction condition it is possible to use such process for carbon-carbon bond formations involving a double bond, aromatic ring or even a classically inactive C-H bond. The most important advantage the present method offers, of course, is the fact that preparation of a large number of bridged-ring systems, the fabrication of which would otherwise require a long sequence of synthetic transformations, can be efficiently accomplished in a single operation by diazomethyl ketone alkylation reaction. Furthermore, it is quite obvious that this reaction has a wide scope for extension to other types of complex natural products.

Acknowledgements

URG is indebted to his colleagues, whose names are listed in the references, for participation in the above studies performed by his group. It is mostly their hard works, clear understanding and experimental skills that have proven decisive both in the formulation of the projects and their executions in the laboratory to a successful conclusion. The financial support from Science and Engineering Research Council/D.S.T. Scheme under Grant No. 23 (3p-8)/81-STP/II for extension of some of these works is gratefully acknowledged.

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Organic synthesis *via* photoinduced hydrogen and electron transfer reactions

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Abstract. Synthetic utility of photoinduced intramolecular hydrogen transfer reactions of ketones, amides, imines, nitrites and nitro compounds is highlighted by illustrative examples. Role of light-initiated electron transfer from amines, mercaptans, aryl groups and from lithiated ketones, amides and imines in reactions of synthetic interest is discussed.

Keywords. Ketones; amides; imines; nitrites; nitro compounds; photocyclisation; benzo-phenanthridines; berberines; aporphines.

1. Introduction

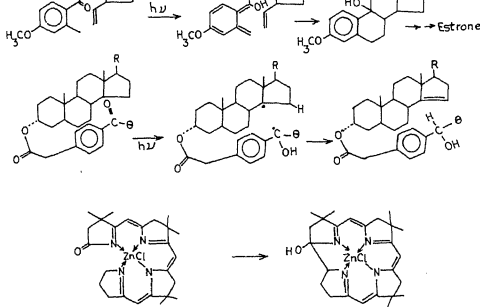
Absorption of light by an organic molecule promotes it to a relatively high energy state and therein lies the strength as well as the weakness of photochemistry as a synthetic tool. Whereas a desired reaction pathway which is thermally inaccessible can become available in the excited state many side reactions may also occur from it. Nevertheless, numerous photoreactions showing good stereo-, regio-, and chemoselectivity have been discovered. The present article is intended to highlight the utility of such reactions for synthesis of complex organic molecules. It is limited only to transformations which involve intramolecular hydrogen or electron transfer as the primary photoprocess. Thus many photoreactions of proven synthetic utility like cycloadditions, electrocyclic ring closures and rearrangements (Wender and Howbert 1982; Oppolzer and Godel 1978; Schultzy *et al* 1977; Ninomiya and Naito 1981) are not covered. Further, the examples are chosen primarily from author's own area of interest *viz* the photochemistry of nitrogen containing functional groups.

2. Hydrogen transfer reactions

On irradiation, functional groups containing oxygen, sulphur and nitrogen multiple bonds can abstract hydrogen from a suitable donor inter or intramolecularly. The latter process is often followed by fragmentation or ring closures of synthetic importance as illustrated below for some classes of compounds.

2.1 Ketones

Photoreactions based on intramolecular hydrogen abstraction are efficient and synthetically useful if a six-membered transition state is involved (Quinkert *et al* 1980). However factors like framework rigidity (Paquette *et al* 1983), solvent-induced folding



distant hydrogen atoms into a disposition favourable for abstraction resulting in 'remote functionalization'.

2.2 Amides

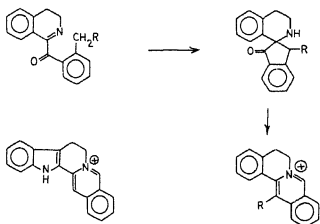
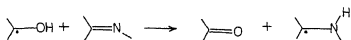
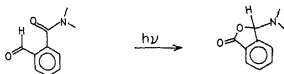
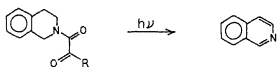
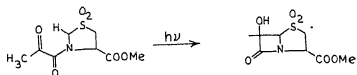
As compared to ketones carboxylic acid derivatives show less proclivity for hydrogen abstraction (Coyle 1978) but rich photochemistry is associated with imides (Kanaoka 1978). In α -ketoamides also hydrogen abstraction is facile and may be followed by a ring closure to a β -lactam (Henry-Logan and Chen 1973; Johansson *et al* 1976) or a α -lactone (Aoyama *et al* 1983).

The diradical initially formed from a α -ketoamide can also undergo a Norrish type-II fragmentation (Aoyama *et al* 1981) but in the case of tetrahydroisoquinoline derivatives further oxidation of the nitrogenous segment is observed (Kessar *et al* 1978). This aromatisation is of mechanistic and synthetic interest due to complications observed during dehydrogenation (Sainsbury *et al* 1969). The vinalogous benzamides with an ortho aldehydic group furnish, on irradiation, amino-lactones, presumably through a 1,5 hydrogen transfer (unpublished results from this laboratory).

2.3 Amines and imines

Many a claimed photoreductions of Schiff bases have been shown to be caused through 'chemical sensitisation' by carbonyl impurities (Padwa 1977; Pratt 1977).

The lack of photoinitiated hydrogen abstraction in imines has been variously attributed to energy dissipation through rapid *cis-trans* isomerisation, $\pi\pi^*$ character of the excited state or the lower strength of the incipient NH bond (Padwa 1977; Pratt 1977; Ohta and Tokumaru 1974). Whatever the reasons for the absence of this photoreactivity in imines, the methodology dependent on it is not available for heterocyclic synthesis. However, recently it has been shown that certain α -ketoimines do undergo phototransformations leading to spirobenzyl isoquinoline and berberine



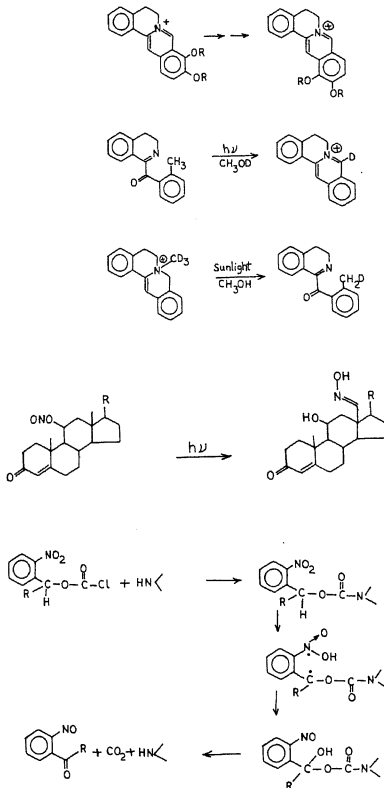
alkaloids (Kessar *et al* 1978). The procedure has been extended to synthesis of indole alkaloids also (Hirai *et al* 1983).

The above reaction when used in conjunction with a known photodegradation of erberine derivatives (Wu *et al* 1978) can bring about an intriguing transposition of D ring substituents of these alkaloids (Kessar *et al* 1982). Mechanisms of both the involved photoreactions have been investigated by deuterium labelling experiments (Kessar *et al* 1982).

4 Nitrites and nitro compounds

Barton reaction (Barton and Akhtar 1962) is an outstanding example of the synthetic utility of photochemical reactions, although here the hydrogen abstraction step may not be occurring on the excited state surface.

Nitro compounds also serve as useful photolabile amine protecting groups



3. Electron transfer reactions

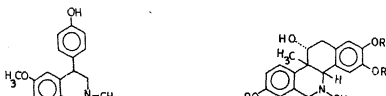
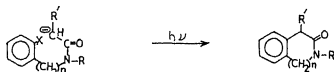
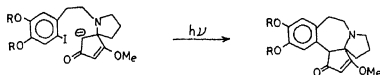
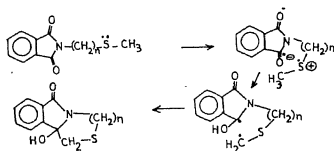
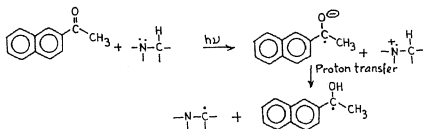
In photoinduced electron transfer reactions, back electron transfer is an energy wasting process. Nature has its own mechanism for overcoming it and in artificial solar energy utilisation also ingenious procedures have been devised to minimise it (Whitten 1980). For a synthetically efficient reaction, electron transfer should be followed by a fast event like loss of a nucleofuge from the receptor or of a proton from the donor. A few such examples involving different functional groups are given below.

1 Ketones and amides

ven carbonyl triplets with a $\pi\pi^*$ character which are generally unreactive in hydrogen abstraction can be efficiently reduced by amines through electron transfer followed by proton transfer (Cohen *et al* 1973). Unfortunately, in the case of aminoketones intramolecular proton transfer is inefficient (Wagner and Ersfeld 1976) and not many reactions of synthetic import have been reported. However, electron transfer from a sulphur atom followed by intramolecular proton transfer has been invoked to explain the formation of medium and large ring systems on irradiation of certain imides (Sato *et al* 1976).

A mechanism involving electron transfer from the nitrogen atom has also been proposed for γ -hydrogen abstraction in α -ketoamides (Aoyama *et al* 1983). Evidence for bimolecular electron transfer in pyruvates has been adduced recently (Davidson *et al* 1983).

Light-promoted electron transfer from enolate anions to aryl halides has been invoked to explain the photoinduced $S_{RN}1$ reactions (Bunnet 1978). An intramolecular



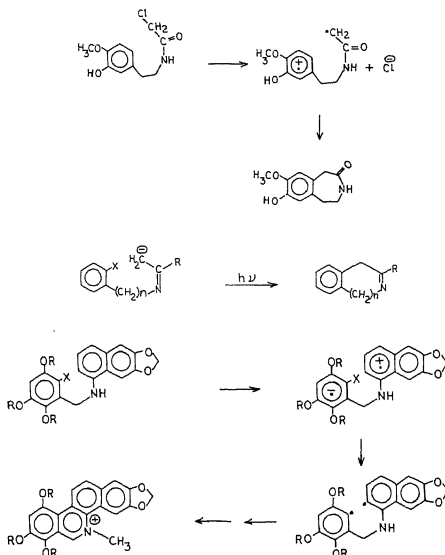
transfer-mediated cyclisation of metalated amides constitutes the key step in the synthesis of cherylline and corynoline-type alkaloids (Kessar *et al* 1981).

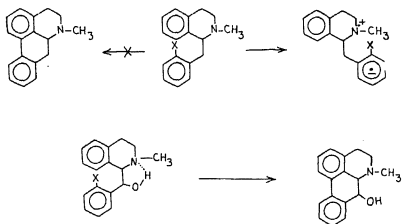
Witkop reaction which is very useful for synthesis of benzazepinones is claimed to entail electron transfer in the reverse direction *i.e.* from the aromatic moiety to the chlorocarbonyl function (Yonemitsu *et al* 1968; Hamada *et al* 1977).

3.2 Amines, imines and enamines

Metalated imines have been found to undergo photocyclisation (unpublished results from this laboratory) in a manner similar to that of carbonyl enolates. This reaction can open up convenient routes to many alkaloidal structures.

Although the nucleophilicity of the enamine carbon atom is well established, photocyclisation based on intramolecular electron transfer to aryl halides could not be induced in these compounds (unpublished results from this laboratory). In contrast, irradiation of the corresponding aromatic amines leads to ready ring closure (Mizuno *et al* 1973). Based on this observation, efficient syntheses of chelilutine and sanguilutine were carried out (Kessar *et al* 1977) to settle the controversy regarding the placement of alkoxy groups in this set of alkaloids (Ishii *et al* 1975). This route has been extended to





the synthesis of macarpine which carries six alkoxy groups on the benzophenanthridine nucleus (Takao *et al* 1981).

Finally, success of certain photoreactions may hinge on preventing the electron transfer process. For example, lack of aporphine formation on irradiation of ortho-halogenated benzyloisoquinolines has been ascribed to a deleterious electron transfer from the nitrogen atom (Kessar *et al* 1981). A strategem for preventing this, and for locking the aryl moieties in close proximity, is based on introduction of a hydrogen bonding group. Synthesis of oliveridine and related alkaloids could thus be achieved readily (Kessar *et al* 1980; Kessar *et al* 1983).

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Strategies of synthesis based on dihydrobenzenes

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Abstract. 1-Methoxycyclohexa-1,4-dienes are readily available from the metal-ammonia-alcohol reduction of aromatic ethers. The use of these dihydrocompounds in the synthesis of a variety of natural products is reviewed.

Keywords. Dihydrobenzenes; synthesis; methoxycyclohexa dienes; selective reactions.

1. Introduction

Reductions of substituted benzenes with alkali metal, alcohol in liquid ammonia, or similar reagents (Birch and Subba Rao 1972) yield with ease a unique set of substituted cyclohexa-1,4-dienes. They have unconjugated double bonds specifically oriented in relation to substituent positions. They act as sources of a further set of unique oriented conjugated dienes, particularly those carrying a 1-OR group. The positions of the hydrogens added in the initial reductions and consequently of the two unconjugated double bonds depend on the nature and position of the substituents. Reduction occurs 1,4- with CO_2H , SiMe_3 , or in some cases $-\text{COR}$ and 2,5- with alkyl, OMe , NR_2 and similar substituents.

A number of uses of cyclohexa-1,4-dienes have been described in the literature, with particular emphasis on the favourable properties conferred by alkoxy groups. The 1-alkoxycyclohexa-1,4-diene series was originally investigated (Birch 1974, 1975) in order to synthesise analogues of steroid hormones (Birch 1950; Djerassi *et al* 1954).

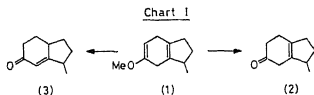
The methoxycyclohexadienes are synthetically useful in many ways because of their valuable and unique structural features which comprise: (i) The directed enol-ether double bond, which has many synthetic equivalents; the ability to make distinctions, direct and indirect, between the reactivity of an enol ether bond and the other present. (ii) The diene system and its reactions in the form of unconjugated, and conjugated, with the effects of alkoxy group on transformations of products. The reactions of dienes as unconjugated include the ability to form a regiospecific carbanion formation without the presence of anion stabilizing groups or aided by groups such as CO_2R and Ph , while the conjugated dienes are useful in the Diels-Alder and Alder-Rickert reactions.

Because of their structural versatility and easy availability, the methoxycyclohexadienes have been a favourite choice as starting materials in synthetic organic chemistry. In this review, it is proposed to discuss some of our own recent work involving the strategies of synthesis of a number of natural products using methoxycyclohexa dienes as starting materials. The reductions of aromatic systems with metal-ammonia or related reagents will not be discussed except to note that the method makes

available many derivatives with specifically oriented unsaturation and has virtually displaced the high pressure catalytic reduction of aromatic systems for synthetic purpose.

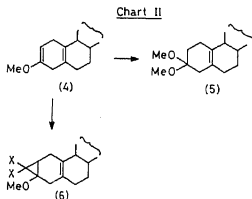
2. Selective reactions on One double bond and the consequences

The more electron rich enol-ether double bond reacts preferentially with electrophilic reagents. Proton additions to an enol-ether double bond afford the β,γ -unsaturated cyclohexenone without effecting the other double bond or α,β -unsaturated cyclohexenone with the isomerization of the other double bond depending on the reaction conditions. These processes are very well known. An example is the conversion of the diene (1) to (2) or (1) to (3) which were required (Pramod and Subba Rao, Unpublished) as important intermediates in some of our synthetic projects.



The enol-ether converted readily into a ketal by the action of an alcohol and a trace of acid without affecting the other double bond (Birch *et al* 1964), which can be used to protect the carbonyl equivalent and reactions can be carried out on the remaining double bond. An example is the conversion of (4) to (5) which was employed (Birch *et al* 1964) as a general method for introduction of angular methyl groups.

The addition of a dihalocarbene can be made selective for the enol-ether double bond and the resulting adducts (6) have several applications (Birch *et al* 1963, 1964; Birch and Keeton 1968).



An enol-ether double bond is also susceptible to selective oxidative fission having the remaining *cis*-double bond untouched in the product. This type of procedure has been used to form synthetic precursors of cecropia hormone, losalocid-A and ionophore antibiotic A-23187 (Corey *et al* 1968; Nakata *et al* 1978). Making use of this method of selective oxidation of one of the double bonds, a very important C_7 synthon (7, 8) has been made (Pramod *et al* 1984) which served as a key intermediate in the synthesis of polyene natural products like, sex pheromones, vitamins A etc. Based on a similar strategy of cleaving one or two double bonds by ozonolysis, the anisole ring or

Chart III

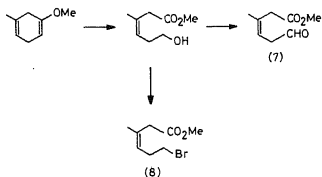
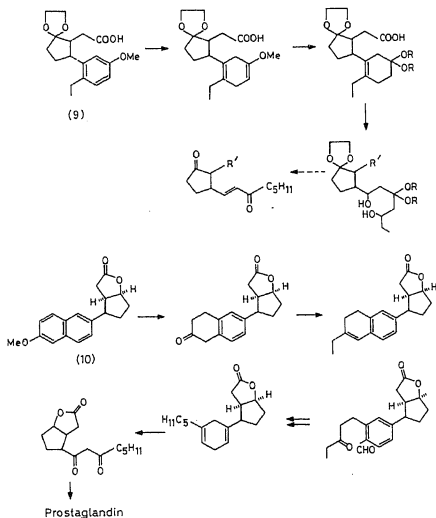


Chart IV



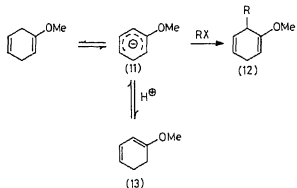
methoxynaphthalene group can act as a stored prostaglandin side chain following the sequence from (9) (Birch *et al* 1984b) and (10) (Ramanathan 1984) respectively.

Both the double bonds can also be cleaved by ozonolysis, the first example being the conversion of 2,5-dihydro-*m*-xylene into acetylacetone (Birch 1944), thus leading to the synthesis of polyketides.

3. Reactions as a diene

ability to lose a doubly allylic proton on treatment with base to give a regionally defined mesomeric C-5 anion (11). Presence of 1-methoxy and especially of 1,5-dimethoxy groups, has an acidifying effect (Birch 1947a, 1950) and the loss of proton is adjacent to -OMe only. Kinetically-controlled protonation or alkylation of U-shaped anions takes place principally or entirely at the central carbon (Birch 1947a, b; 1950). Reversible additions lead (Birch 1947a, 1950) to equilibration resulting in the thermodynamically more stable diene. This was the first method of producing the 1,3-diene (12) (about 75%) in equilibrium with the 1,4-diene (11) (25%) using a small proportion of base. The conjugated diene yields with base the same anion as the unconjugated one. This idea was successfully exploited for the deconjugation of an α,β -unsaturated ketone via the enolate anions in the conversion of cholesta-4-enone into cholest-5-enone (Birch 1951).

Chart V



The most useful synthetic application so far involves the formation of a new carbon-carbon bond at the central position by alkylation (Birch 1947a, 1950; Pramod *et al* 1983), arylation (Pramod *et al* 1983) and Michael type reaction (Subba Rao *et al* 1980). Only one carbon-carbon bond can be formed, probably because of the reduced acidity due to substitution. This has the advantage of preventing over-reaction, but the disadvantage is that the quaternary carbon cannot be formed in this series. This type of alkylation leads to dienes which are difficult to obtain by any other methods. An exception is the 2,6-dimethoxybenzoic acid series, where -OMe directs the reductive alkylations into the 1-position even when substituted. However, such aromatic precursors are less readily available.

The products (12) of reductive alkylation have two types of synthetic equivalents according to their subsequent treatment. One is the aromatic anion (14) following the treatment with lead tetraacetate (LTA) which aromatizes the 1,4-diene quantitatively. The other is the equivalent of the enolate anion (15), following gentle acid hydrolysis. The alkylated dienes (12) themselves have direct synthetic uses in Alder-Rickert reaction as noted below.

Low acidities in the alkylcyclohexadiene series can be overcome by the attachment of a group to localise the anionic charge, such as carboxyl, even as the salt (Birch 1947a, 1950). Carboxyl has the advantage that it is possible to remove that group (Birch *et al* 1951) once the purpose is served.

The 2-methoxybenzoic acid series can undergo alkylation (Taber 1976; Birch and Slobbe 1977, Hook *et al* 1979; Bedri *et al* 1969) or Michael-type reactions (Subba Rao *et al* 1980). In -OMe series, synthetic use of -COOH group is unnecessary even though

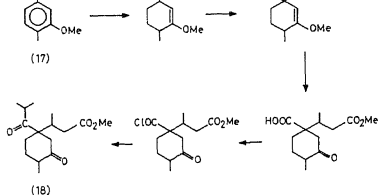
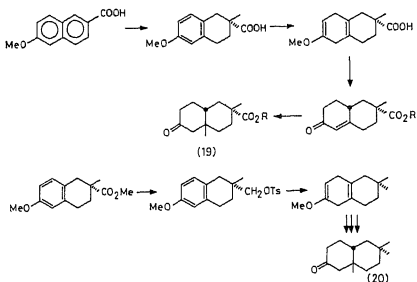


Chart IX



(ii) *Conjugated*: The most important reactions of the methoxycyclohexadienes are as components in various types of Diels-Alder reaction. These reactions are particularly important in forming six-membered rings by two carbon-carbon bonds. These reactions are insensitive to steric effects due to the substitution of the diene, enabling, for example, the production of quaternary carbon centres. There are now very well known rules of stereochemistry governing the lateral junction of two components (Diene and dienophile), for example, the configuration of the dienophile is retained, subject to certain orientation rules (Birch 1950).

Unlike of methoxycyclohexa-1,4-dienes, the alkylcyclohexa-1,4-dienes cannot be conjugated readily by charge transfer complexation or by high pressure to undergo Diels-Alder reactions *in situ*. Whereas 1-methoxycyclohexa-1,4-dienes can be readily used *in situ* for the reactions under high pressure (*i.e.* sealed tube reactions) or by catalytic amount of dichloromaleic anhydride for ready conjugation in the reaction mixture. This *in situ* process has the advantage that all the dienes present are positively used. However, the problem of conjugation of alkyl cyclohexa-1,4-dienes to the cyclohexa-1,3-dienes has been partially solved by the use of $(\text{MeCN})_3\text{Cr}(\text{CO})_3$ as catalyst (Birch and Day 1984).

The major synthetic advantage of using Diels-Alder reaction with cyclic dienes is that it generates bridged bicyclic globular products which are valuable synthetic inter-

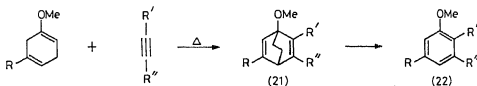
specifically. The first requirement is met by the Alder-Rickert reaction, and the second by a fission based on the presence of a bridge head-OMe or an equivalent in retro-aldol fashion.

The importance of 1-methoxy group rests also on its ability to direct the regiochemistry of the addition. Whatever the substitution on the diene or the dienophile the activating group of the latter (CO_2Me , CN , COR etc.) is found adjacent to $-\text{OMe}$ in the product. The easy availability of a very large number of substituted cyclohexa-1,4-dienes and their reduction alkylated products provide a range of cyclic dienes with wide orientation of substituents shows the importance of these dienes which are otherwise difficult to obtain for the Diels-Alder reaction.

(a) *The Alder-Rickert reaction for synthesis of aromatic compounds*

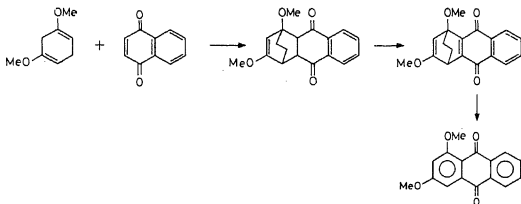
A typical Alder-Rickert reaction is shown in Chart X. The structural requirement for this reaction is a 2,5- C_2 -bridge across a cyclohexa-1,4-diene (21) pyrolysis then, readily removes the ethano bridge as an olefin leaving a benzenoid ring (22). The nature of the bridge does not matter since it is lost. Diels-Alder reaction is the best source to get such unsaturated bridged ring structures by the addition of activated acetylenes with cyclohexa-1,3-dienes.

Chart X



In cases of quinone as the dienophile, addition of quinone to a diene, followed by aromatization, or oxidation to quinone back provide the appropriate activation and elimination of the bridge as shown in the Chart XI.

Chart XI



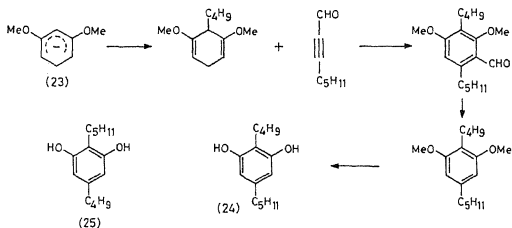
The presence of 1-methoxy on the diene has its own advantages, as pointed out earlier. The intermediate bicyclic adducts (21) from acetylenes can be isolated by carrying out the reaction at room temperature and 15 kbar pressure (Subba Rao and Ramanathan 1984; Subba Rao and Kanakam 1984). With this reaction many aromatic

polyketides derivatives with varying substituents unusual positions can be easily prepared. In this regard it is correct to say that the use of 1-methoxycyclohexadienes is equivalent to oriented addition of four carbons, carrying a possible variety of substituents, laterally to the two carbons of an acetylene to complete the aromatic skeleton.

The Alder-Rickert process in this series had initially given, by accident, several simple polyketide derivatives (Birch *et al* 1954). Later, using the similar strategy, mycophenolic acid (Birch and Wright 1969) a fungal product, and lasiodiplodin (Birch *et al* 1970) have been synthesised. Some other detailed examples are given below.

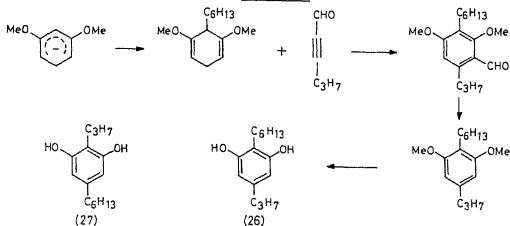
(1) *Stemphol* (24). This synthesis is an example of the use of an anion (23) as the basis of easy production of starting materials. The structure of the stemphol (24) was incompletely known when the synthetic work was carried out (C_4H_9 and C_5H_{11} interchangeable) and both isomers (24 and 25) were readily synthesised (Ramanathan *et al* 1984) and that shown being identical with authentic material.

Chart XII



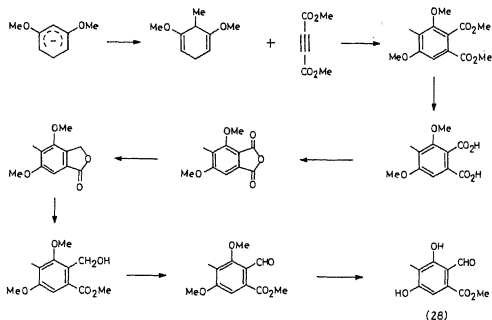
(2) *Antibiotic DB 2073* (24). Similar to the synthesis of stemphol (24) and its isomer (25), starting with the mesomeric anion (23) the antibiotic 2073 (26) and its isomer (27) have been synthesised (Ramanathan *et al* 1984).

Chart XIII



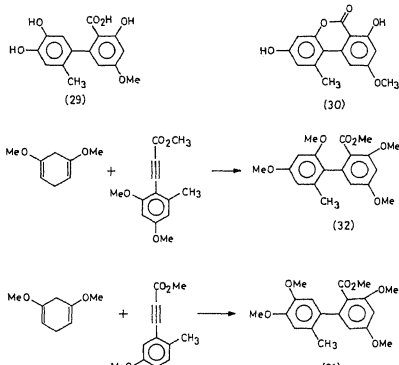
(3) *3,5-Dihydroxy-2-formyl-4-methylbenzoate* (28). Sassa and Miura (1973) have isolated a root growth stimulant as metabolite from fungus. This root growth stimulant has been synthesised (Murthy 1981) by the strategy involving the reductive alkylation and Alder-Rickert reaction.

Chart XIV



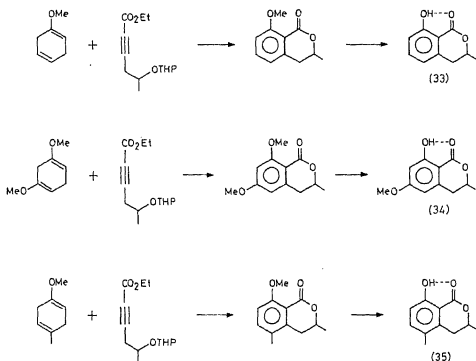
(4) *Altenusin* (29) and *Alternariol* (30). *Altenusin* (29) (Rosett *et al* 1957) and *alternariol* (30) (Rarstrick *et al* 1953) the fungal metabolites having 6-aryoresorcyate skeleton, are known to possess antibacterial activity. Synthesis (Kanakam and Subba Rao 1984) of tetramethyl altenusin (31) and tetramethyl alternariol (32) was accomplished by this strategy.

Chart XV



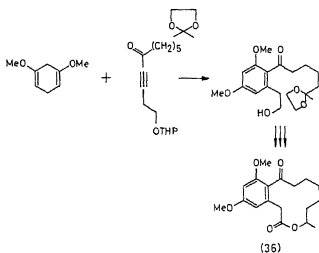
(5) *Mellein* (33), *6-Methoxymellein* (34) and *5-Methylmellein* (35). Based on the Alder-Rickert reaction, the isocoumarin natural products mellein, 6-methoxymellein and 5-methylmellein have been synthesised (Mani and Subba Rao 1984).

Chart XVI



(6) *Curvularin* (36). This is a naturally-occurring macrolide and notable for its antifungal and antibiotic activity (Mirrington *et al* 1966; Mecapra and Scott 1964). This 12-membered macrocycle fused to aromatic ring has been synthesised recently (Wasserman *et al* 1981). Based on the Alder-Rickert reaction an easy and efficient synthesis of this molecule has been achieved (Mani and Subba Rao 1984).

Chart XVII

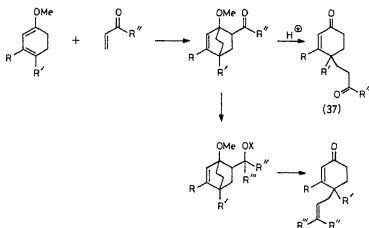


In addition to all the examples described above many derivatives of natural

(b) Retro-Aldol type fissions

More often in the organic synthesis, not only making new carbon-carbon bond is important but the cleavage of a carbon-carbon bond also plays a very crucial role. Eschenmoser fragmentation (Eschenmoser *et al* 1967) reaction is a classical example where acetylenic aldehydes are prepared from α,β -unsaturated cyclohexenones. The bicyclic-bridged systems with bridge head-OMe are readily prepared by Diels-Alder reaction of 1-methoxycyclohexadienes play an important role in the organic synthesis. The cleavage of one of the carbon-carbon bond formed in the above process yield very useful synthetic intermediates (37) as illustrated in Chart XVIII.

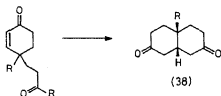
Chart XVIII



This cleavage process has been affected under mild conditions probably due to the release of the strain which accompanies the breakdown of the bridged ring system. Acid-catalysed ring opening involves a retro-aldol fission initiated by protonation of the carbonyl group adjacent to the bridgehead -OMe group. Appropriate carbonium ion for initiating ring fission can also arise from the ionisation of the C-O bond as a tosylate, or by the acid treatment on a tertiary alcohol. However, adducts from acrylic esters or nitrile do not undergo the reaction presumably because of lack of protonation of these groups.

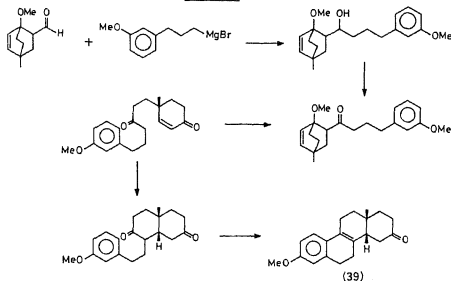
The products obtained by this type of fission, like compound (37) having reactive functions in their side chain undergo with suitable conditions, cyclisation with the cyclohexenone system to give *cis*-decalin system (38) (Birch *et al* 1964), stereospecifically in addition to some other products. Some other similar reaction of cyclisations were reported and their stereochemistry also elaborately discussed (Johnson *et al* 1964; House *et al* 1965).

Chart XIX



Based on this retro-aldol type fission, followed by cyclisation, a potential intermediate (20) for the synthesis of aromatic steroids has been achieved (Uma Sheriff and

Chart XX

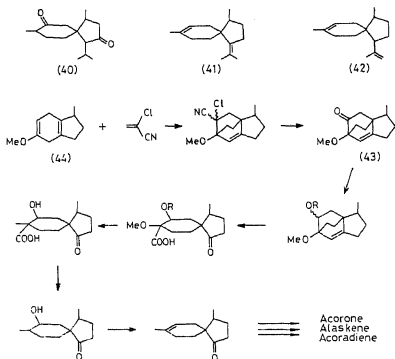


Subba Rao 1984). With this another new method of building aromatic steroid by AD $\rightarrow$ ABCD approach has been accomplished.

(c) Other reactions based on Diels-Alder adducts of methoxycyclohexadienes

Adducts form from methoxycyclohexadienes by Diels-Alder reaction have been extensively used in the organic synthesis. One of the recent examples is the synthesis of bazzanene, α and β -barbalenes and gymnomitral by Sho Ito (1980). The ease of formation of quaternary centres, presence of double bond and the substituent groups of diene and dienophile in the adduct, made them very potent synthons for many natural product synthesis. The presence of bridgehead methoxyl group may not be

Scheme XXI

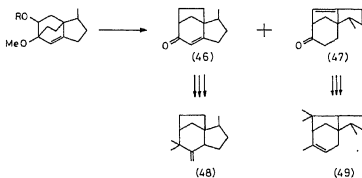


and increase the rate of addition. There are many natural products where (2.2.2)bicyclo system is apparent in their structures.

The presence of a double bond in the (2.2.2)bicyclo adduct makes these adducts to be as potent intermediates for the synthesis of spiro systems. Oxidative cleavage of the double bond in such systems yield spiro skeleton. This method has been successfully used (Pramod and Subba Rao 1984) in the synthesis of spiro (4:5) decane sesquiterpenes like Acorone (40), Alaskene (41) and Acoradiene (42). The adduct (43) which was prepared by the regioselective addition of ketone equivalent to methoxydiene (44) followed by hydrolysis has been used to prepare a key intermediate (45) for the synthesis of the spiro sesquiterpene natural products.

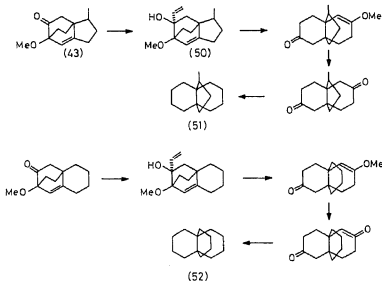
The bridgehead -OMe permits rearrangement of a (2.2.2)bicyclo system into a (3.2.1)-bicyclo system, presumably due to the release in the ring strain (Alfaro *et al* 1974). This rearrangement has been extended to zizaene (48) and cedrene (49) sesquiterpenes (Pramod and Subba Rao 1982; Pramod *et al* 1984) via their intermediates (46) and (47) respectively.

Scheme XXII



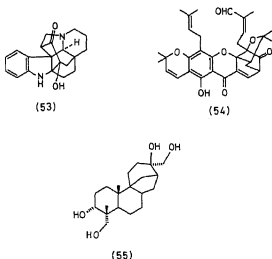
Using the adduct (43) a new and efficient synthesis (Pramod and Subba Rao 1982) of 11-methyl[4.4.3]propellane (51) has been prepared by the base catalysed rearrangement of the carbinol (50). Similarly the [4.4.4]propellane (52) has also been prepared.

Scheme XXIII



It is clear from the above discussion that cyclohexa-1,4-dienes are highly versatile building blocks whose further use in organic synthesis, particularly in the realm of naturally occurring substances, should prove of immense value. The technique of reductive alkylation followed by cycloaddition has been extended to the synthesis of natural products which contain the (2.2.2)-bicyclic system or its equivalents. Among these compounds the synthesis of kopsine (53), morellin (54) and aphidicolin (55) is in progress in our laboratory.

Chart XXIV



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Reaction of N-acylisatins with *o*-aminophenol and *o*-aminothiophenol¹

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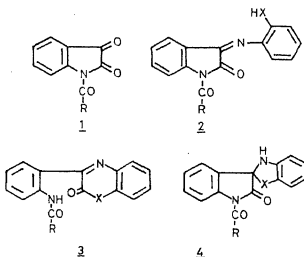
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Abstract. The reaction of N-acylisatins 1a–1d with *o*-aminophenol gives the benzoxazinones 3a–3d. With *o*-aminothiophenol, 1a and 1b give a mixture of products from which were isolated 2f, 3d, 3e, 5a, 6 and 7.

Keywords. Benzoxazinones; benzothiazinones; benzthiazole.

1. Introduction

The reaction of N-acylisatins with aromatic 1,2-diamines has been shown to yield 3-*o*-acylaminophenyl-2H-quinoxalin-3-ones (Joshi *et al* 1983). We report here the reaction of N-acylisatins with *o*-aminophenol and *o*-aminothiophenol.



	X	R
a :	O	CH ₃
b :	O	CH ₂ CH ₃
c :	O	CH ₂ CH ₂ CH ₃
d :	O	C ₆ H ₅
e :	S	CH ₃
f :	S	CH ₂ CH ₃

¹ Communication No. 713 from Hindustan CIBA-GEIGY Research Centre.

2. Results and discussion

For the reaction product m.p. 169–170°, obtained by the condensation of N-acetylisisatin (**1a**) with *o*-aminophenol, structure (**2a**) had been assigned previously (Parisi 1953). We find that in ethanol as well as in acetic acid, the same product, m.p. 179°, is formed, the structure of which should be revised to **3a**. The compound is insoluble in cold 10% aqueous alkali and dissolves only on warming. The IR spectrum, $\nu_{\max}$ 1740, 1675 cm^{-1} , does not agree (Joshi *et al* 1983) with **2a** but is in good agreement with the reported spectrum of 3-phenyl-2H-1,4-benzoxazin-2-one (rep. $\nu_{\max}$ 1740 cm^{-1}) (Chioccora *et al* 1976). Its ^1H NMR spectrum shows the methyl of $\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ at δ 2.1 ppm in contrast to N-acetylisisatin (**1a**) where it appears at δ 2.75 ppm, supporting the structure **3a**, involving the opening of the N–C₂ bond of isatin.

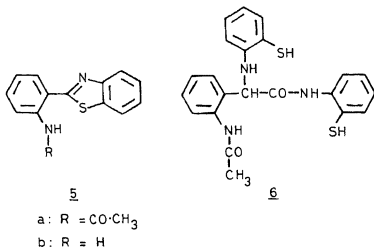
The homologues **1b** and **1c** gave **3b** and **3c** respectively. In **3b**, the $\text{N}\cdot\text{CO}\cdot\text{CH}_2$ appears in the ^1H NMR spectrum as a quartet at δ 2.4 ppm and in **3c** as a triplet at δ 2.2 ppm. In **1b** and **1c**, this methylene appears near δ 3 ppm. N-Benzoylisisatin (**1d**) similarly gives **3d**.

Compounds **3a**–**3d** show the molecular ion peaks in their mass spectra and a strong M–28 peak due to loss of CO as has been observed in the case of 2H-1,4-benzoxazin-2-ones (Reichen 1977).

The reaction of N-acylisisatins with *o*-aminothiophenol, which is not reported in literature, was more complicated. Several products were formed as seen by TLC and chromatographic separation yielded only some of them in pure state.

The reaction of **1a** with *o*-aminothiophenol in acetic acid gave **3e**, insoluble in cold 10% aqueous alkali, $\nu_{\max}$ 1695 cm^{-1} (Ar–CO–S–Ar, reported $\nu_{\max}$ 1685 cm^{-1}) (Nyquist and Potts 1959). Its ^1H NMR, δ 2.25 ppm (3H, s, $\text{NH}\cdot\text{CO}\cdot\text{CH}_3$), supports the N–C₂ cleavage. The homologue **1b** similarly gives **3f**, its ^1H NMR spectrum showing the $\text{NH}\cdot\text{CO}\cdot\text{CH}_2$ methylene as a quartet at δ 2.4 ppm.

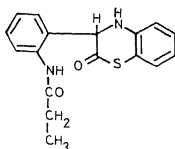
From the reaction of **1a** with *o*-aminothiophenol in ethanol, two products were isolated. The less polar one, m.p. 120°, $\text{C}_{15}\text{H}_{12}\text{N}_2\text{OS}$ (M^+ at m/e 268), ^1H NMR: δ 2.25 ppm (3H, s, $\text{NH}\cdot\text{CO}\cdot\text{CH}_3$), was identified as the benzthiazole (**5a**). An authentic sample of **5a** was prepared by acetylation of the known **5b** obtained by reaction of anthranilic acid with *o*-aminothiophenol (Hein *et al* 1957).



Compound **5a** could have arisen from **4e**. Decarbonylation of **3e** is less likely under the conditions of the experiment since 3-phenyl-2H-1,4-benzoxazin-2-one yields

The more polar product of the reaction mixture from **1a**, m.p. 215°, $C_{22}H_{21}N_3O_2S_2$, is soluble in 10% aqueous alkali and insoluble in 2N HCl, $\nu_{\max}$ 1710, 1680, 1650 cm^{-1} . Its 1H NMR shows a singlet at δ 2.05 (3H, $NH \cdot CO \cdot \underline{CH_3}$), a singlet (1H) at δ 5.15 (benzylic CH) and 12 aromatic hydrogens as a complex multiplet. The compound is assigned structure **6**, its formation involving reaction of one mole of isatin with two moles of thiophenol and also reduction of the azomethine double bond by thiophenol.

From the reaction of the homologue (**1b**), in addition to **3f**, two compounds were isolated in poor yields: **2f**, m.p. 145°, $C_{17}H_{14}N_2O_2S$ (M^+ at m/e 310), soluble in 10% aqueous alkali, $\nu_{\max}$ 3360, 1770, 1700 cm^{-1} . 1H NMR: δ 3 (3H, q, $N \cdot CO \cdot \underline{CH_2}$) and **7**, m.p. 215°, $C_{17}H_{16}N_2O_2S$ (M^+ at m/e 312), insoluble in alkali, $\nu_{\max}$ 1680, 1660, 1650 cm^{-1} , 1H NMR: δ 2.4 (3H, q, $NH \cdot CO \cdot \underline{CH_2}$), 5.1 (1H, s, benzylic CH) ppm. Compound **7** is evidently formed by reduction of the azomethine bond by thiophenol.

**7**

3. Experimental

Melting points are uncorrected. 1H NMR spectra were recorded in $CDCl_3$, except for **6a** which was run in a mixture of $CDCl_3 + DMSO-d_6$, on a Varian EM 360 L spectrometer. Mass spectra were determined on a Varian Mat CH 7 instrument at 70 eV utilizing direct insertion. IR spectra were taken in nujol on a Perkin-Elmer Infracord instrument.

Table 1. Physical constants of compounds prepared.

Sl. No.	Compound	Mol. formula	Mol. wt.	m.p.°C	Solvent of crystallisation
1	3a	$C_{16}H_{12}N_2O_3$	280.3	179	MeOH
2	3b	$C_{17}H_{14}N_2O_3$	294.3	180	"
3	3c	$C_{18}H_{16}N_2O_3$	308.3	147	"
4	3d	$C_{21}H_{14}N_2O_3$	341.3	208	"
5	3e	$C_{16}H_{12}N_2O_2S$	296.3	128	C_6H_6 -hexane
6	3f	$C_{17}H_{14}N_2O_2S$	310.3	125	$CHCl_3$ -hexane
7	5a	$C_{15}H_{12}N_2OS$	268.3	120	C_6H_6
8	6	$C_{22}H_{21}N_3O_2S_2$	423.4	215	CH_2Cl_2
9	2f	$C_{17}H_{14}N_2O_2S$	310.3	145	C_6H_6
10	7	$C_{17}H_{16}N_2O_2S$	312.3	215	CH_2Cl_2 -MeOH

3.1 General procedure

A mixture of N-acylisatin (10 mmol) and *o*-aminophenol or *o*-aminothiophenol (10 mmol) was refluxed for 8 hr either in acetic acid (25 ml) or ethanol (25 ml). In the former case, the solution was poured on ice and the crude solid extracted with chloroform. In the latter case, the alcohol was evaporated in vacuo. The crude product obtained by either method was chromatographed over silica gel in the order C_6H_6 , $C_6H_6-CHCl_3$, $CHCl_3$ and $CHCl_3-MeOH$.

The physical constants of the compounds prepared are recorded in table 1.

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Aspects of tautomerism 12—Some causes and consequences of participation in the solvolysis of acid chlorides†

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Abstract. Solvolysis of nine representative half ester acid chlorides in aqueous acetone have been studied. Isomers solvolyse at distinctly different rates and furnish the original acids. Contrary to the well accepted views, no evidence for tautomerism or isomerism between the isomeric pairs of acid chlorides could be detected. In a number of cases alkoxy group participates in the solvolysis of neighbouring acid chlorides. This results in (a) rate enhancement and (b) partial or total shift of the reaction pattern from S_N2 to S_N1 . Isomeric half ester acid chlorides, in the presence of a sufficiently strong Lewis acid, could give the same oxonium salt. Rearrangements observed in the reactions of unsymmetrical 1,2- and 1,3-dicarboxylic acid derivatives could be ascribed to the prior formation of common oxonium salt intermediates in the presence of Lewis acids.

Keywords. Tautomerism; solvolysis; acid chlorides.

1. Introduction

One of the frustrating aspects of the chemistry of unsymmetrical 1,2- and 1,3-dicarboxylic acid derivatives is the lack of positional specificity in their reactions. Recent reports on the synthetic applications of 3-methoxy-phthalic acid derivatives in the synthesis of cytotoxic antibiotic adriamycin and its derivatives have highlighted this problem (Wong *et al* 1973; Reynolds *et al* 1977). It is difficult to predict the outcome of the reactions involving 3-substituted phthalic and similar acid derivatives.

As part of our studies on the influence of neighbouring group effects on the structure and mechanisms, we have examined some of the causes of rearrangements in the reactions of acid chlorides. In an earlier paper (Bhatt *et al* 1979) we had attempted to define the factors responsible for the exclusive formation of the pseudo acid chloride at the expense of the normal isomer. This phenomenon represents participation of an extreme kind. Many features of this type of behaviour are now fairly well understood. However, there exists a substantial body of participation behaviour which creates some amount of confusion. This paper attempts to examine this area.

2. Results and discussion

In a long and definitive paper, Chase and Hey (1952) examined the causes of rearrangements in unsymmetrical 1,2- and 1,3-half ester acid chlorides in great detail.

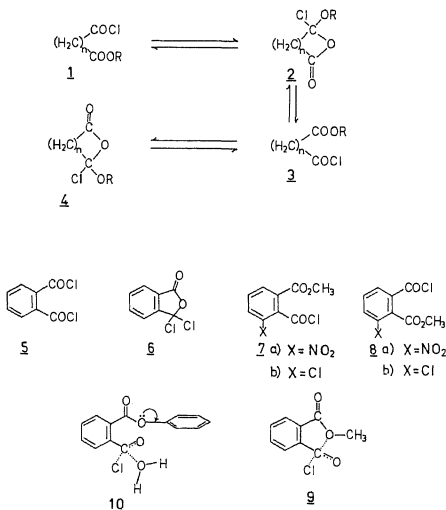
They concluded that these half ester acid chlorides themselves exist in equilibrium (tautomerism), just as symmetrical and unsymmetrical phthaloyl chlorides (Csanyi 1919) (1-4, Chart-1). Subsequent view has more or less congealed and these ideas have come to be accepted as settled facts. They have been widely reproduced in reviews (Jones 1963), advanced treatises (Rodd 1956) and text books (Feiser and Feiser 1961).

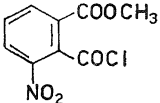
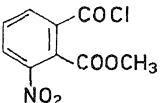
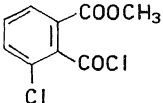
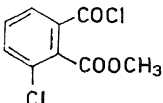
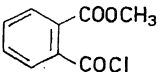
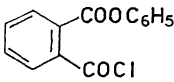
It is well established that the basic patterns of solvolysis of normal and pseudo acid chlorides are different. The former ordinarily solvolyses by a S_N2 path whereas the latter does so by a S_N1 route. We have recently shown that equilibrium between normal and pseudo forms of phthaloyl chlorides ($5 \rightleftharpoons 6$) does not exist under a wide variety of conditions (Bhatt *et al* 1980). We now describe a study of the solvolysis of a few representative half ester chlorides, in aqueous acetone, with a view to finding out whether participation takes place and whether or not they exist in equilibrium.

The solvolysis of isomeric half ester acid chlorides of 3-substituted phthalic acids follow a definite trend. Whereas the acid chlorides (7a, b) solvolysed by a S_N2 path, their isomers (8a, b) do so by a S_N1 mechanism. Also, the rates of solvolysis of isomers are widely different (table 1, figures 1 and 2). It is apparent that electron-withdrawing groups resist development of an electron-deficient centre in the ortho position. No such limitation operates in the case of (8), where such a centre would be in the meta position where it is less subjected to destabilising influence of the electron-withdrawing group.

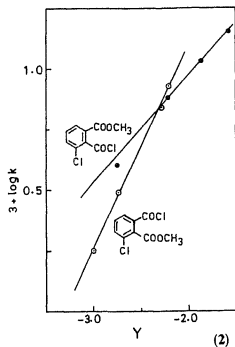
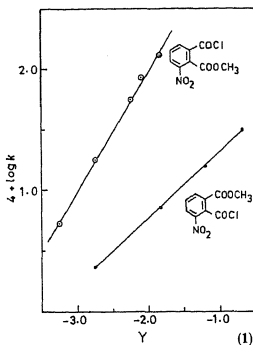
Comparison of solvolysis rates and patterns of phenyl and methyl half ester chlorides

Chart-1



Compound	Percentage of water*	Percentage of acetone*	<i>k</i>	<i>m</i> value
	5	95	2.28×10^{-4}	0.55
	10	90	7.03×10^{-4}	
	15	85	1.59×10^{-3}	
	20	80	3.11×10^{-3}	
	2.5	97.5	5.24×10^{-4}	1.02
	5.0	95.0	1.77×10^{-3}	
	7.5	92.5	5.78×10^{-3}	
	10.0	90.0	1.32×10^{-2}	
	5	95	4.12×10^{-3}	0.44
	8	92	7.51×10^{-3}	
	10	90	1.08×10^{-2}	
	12	88	1.35×10^{-2}	
	4.0	96.0	1.78×10^{-3}	0.89
	5.2	94.8	3.07×10^{-3}	
	7.4	92.6	6.79×10^{-3}	
	8.0	92.0	8.45×10^{-3}	
	2	98	7.19×10^{-4}	1.27
	4	96	2.91×10^{-3}	
	6	94	7.58×10^{-3}	
	7	93	1.36×10^{-2}	
	5	95	4.27×10^{-4}	0.64
	10	90	1.34×10^{-3}	
	15	85	4.17×10^{-3}	
	20	80	1.06×10^{-2}	

* Percentage compositions are volume by volume.



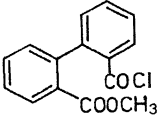
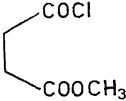
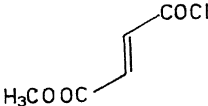
Figures 1 and 2. Plots of Y vs $\log k$ for the isomeric acid chlorides.

of phthalic acid (9) and (10), is particularly instructive. The methyl ester chloride 9 solvolyses about ten times as fast as the phenyl ester chloride 10. Moreover, the reaction pattern shifts from S_N1 in the case of 9 to S_N2 for 10. In the latter the lone pair on the oxygen of the ester function is effectively delocalised with the aromatic ring and becomes unavailable for coordination with the electron deficient species, whereas in the case of the former the lone pair becomes available for participation (table 1, chart 1).

The susceptibility of the reaction rate to solvent polarity change as measured by the m value (Grunwald and Winstein 1948) was used to monitor the changes in the reaction patterns. A m value of 0.6 and less was considered as indicative of S_N2 reaction whereas a m value of greater than 0.6 was taken as evidence for a S_N1 pathway. These criteria have been thoroughly cross-checked with a number of independent evidences like common ion effect, salt effect, solvent isotope effect etc., in similar studies carried out in this laboratory (El Ashry 1977; Bhatt *et al* 1979). We have come to rely on m value as a dependable indicator of the reaction pattern.

The monoester chloride of diphenic acid (11) solvolyses with a m value of 0.42 showing little change from S_N2 pattern and no evidence for participation (table 2). Normal phthaloyl chloride (Bhatt *et al* 1980) and *o*-acetyl salicyloyl chloride (12) (El Ashry 1977) behaved similarly. Also, the monoester chlorides of succinic acid and fumaric acid solvolysed by a S_N2 mechanism as would be expected (table 2). Three analogues of 12 viz *o*-acetamidobenzoyl chloride (15), *S*-acetylsalicyloyl chloride (16) and *o*-acetonylbenzoyl chloride (17) have been examined. None of these showed any evidence of participation (Bhatt and Somayaji 1984; Somayaji 1980).

These results clearly rule out the existence of a dynamic equilibrium between the isomeric half ester acid chlorides. The large number of rearrangements observed with unsymmetrical 1,2- and 1,3-dicarboxylic acid derivatives in Friedel-Craft and other acid

Compound		or water*	or acetone*	K	value
11		3	97	8.62×10^{-5}	0.42
		10	90	2.99×10^{-4}	
		15	85	5.49×10^{-4}	
		20	80	9.55×10^{-4}	
13		4	96	6.31×10^{-3}	0.46
		6	94	1.03×10^{-2}	
		8	92	1.60×10^{-2}	
		10	90	2.16×10^{-2}	
14		4	96	4.69×10^{-3}	0.41
		6	94	6.71×10^{-3}	
		7	93	7.95×10^{-3}	
		10	90	1.34×10^{-2}	

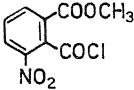
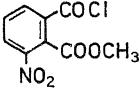
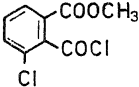
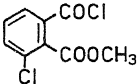
* Percentage compositions are volume by volume.

intermediates formed from the reactions of two pairs of half ester chlorides 7 and 8 with four Lewis acids. The ^1H NMR spectra of the parent acid chlorides showed distinct signals for the methyl groups. When treated with the Lewis acids the signals shifted substantially to a common value (table 3).

The ^{13}C NMR spectra of the complexes obtained from these half ester acid chlorides and Lewis acids showed only three sets of signals for aromatic carbons at 140.68, 130.51 and 128.90 δ , a single signal for the methyl carbon at 53.72 δ and a single signal for both the carbonyl carbons at 167.96 δ . Spectra recorded at low temperatures (0 $^\circ$ and -40 $^\circ\text{C}$) did not show any noticeable deviation from the above mentioned signals thereby ruling out the formation of intermediates (18) and (19) from the isomeric half ester acid chlorides (A, chart 2).

The most reasonable structure for these complexes is the symmetrical oxonium salt formulation (20). That the signal in the ^1H NMR spectra of the complexes did not arise from the reaction of methyl chloride and aluminium chloride was also established. The

Table 3. ^1H NMR data of the Lewis acid complexes of the half ester acid chlorides^a

	Compound	Uncomplexed signal	Signal of the complex with			
			AlCl_3	TiCl_4	SnCl_4	ZnCl_2
7a		4.09	4.60	4.40	4.13	4.09
8a		4.01	4.60	4.40	4.13	4.01
7b		4.00	4.60	4.40	4.10	4.00
8b		3.90	4.60	4.40	4.10	3.90

^a Chemical shifts are in δ (ppm).

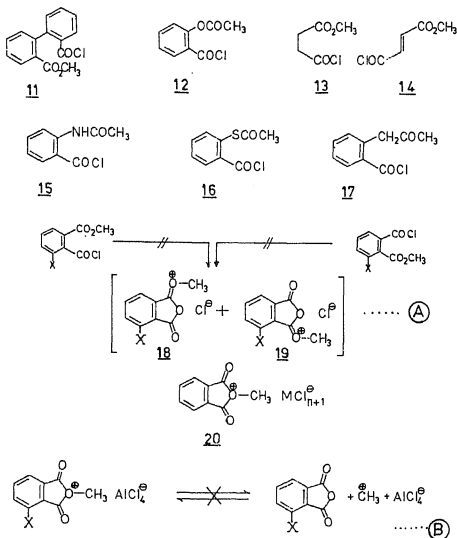
latter shows a signal at 2.95δ unaffected by the presence of phthalic anhydride. It is therefore clear that we are not dealing with an equilibrium of the type *B* (chart 2). Whether one starts from 7 or 8, the product is the same. Any regio-specificity, that would be observed in the reactions of 20 with nucleophiles would be fortuitous.

It is seen from table 3 that $\Delta\delta$, the difference in the chemical shifts for the methyl protons of the complexed and the uncomplexed acid chlorides depends upon the Lewis acid used. This dependence probably reflects its strength. The largest shift in the signals is observed with the strongest of the Lewis acids used *viz* aluminium chloride. Zinc chloride almost does not have any effect on the methyl signal. This is most certainly due to the fact that it is not strong enough to bring about the formation of the oxonium salt.

3. Experimental

The melting points reported are uncorrected. ^1H NMR spectra were recorded on a Varian HA 100D spectrometer. ^{13}C NMR spectra were recorded on a Bruker WH 270

Chart-2



1-Methyl-2-hydrogen-3-chlorophthalate, mp 170°C , and 2-methyl-1-hydrogen-3-chlorophthalate, mp 140°C were prepared as described in an earlier paper (Rao and Bhatt 1980).

Diphenic acid monomethyl ester was prepared according to literature procedure (Graebe 1888), mp 110°C .

Phenyl hydrogen phthalate, mp 102°C , was prepared by fusing phthalic anhydride with phenol (Bischoff and Hedenstrom 1902).

Methyl hydrogen phthalate, methyl hydrogen succinate and methyl hydrogen maleate were prepared by opening the respective anhydrides with methanol.

3.2 Preparation of acid chlorides

The acid chlorides of the half ester acids were prepared by the action of thionyl chloride on the acids. The excess of reagent was removed under vacuum, the last traces being driven off azeotropically with dry benzene. Methyl hydrogen maleate gave monomethyl fumaroyl chloride.

3.3 Preparation of Lewis acid complexes

Titanium chloride complexes were prepared by treating the acid chloride solutions in benzene with an equimolecular amount of titanium chloride. A white precipitate was formed immediately. Benzene was removed under reduced pressure.

Stannic chloride complexes were prepared by refluxing the half ester chlorides in dry chloroform with an equimolecular quantity of stannic chloride for 30 min and removing the solvent under vacuum.

Zinc chloride complexes were prepared by refluxing an equimolecular mixture of the acid chloride and zinc chloride in benzene for 1 hr and removing the excess of solvent under vacuum.

The spectra of the complexes were recorded in a mixture of deuterio chloroform (CDCl_3) and hexadeutero dimethyl sulfoxide (DMSO-d_6).

3.4 Kinetic procedure

The rates of solvolysis of acid chlorides were followed conductometrically. The kinetic procedure employed is essentially the same as reported in an earlier paper (Bhatt *et al* 1979). The rates reported in the present work are at 30°C. The concentration of the acid chlorides used in the kinetic run was 0.02 M unless otherwise mentioned.

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Asymmetric reduction of carbonyl compounds with chiral alkoxyaluminium and alkoymagnesium halides: an overview

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Abstract. A summary of the work on asymmetric reduction of carbonyl compounds with chiral alkoxyaluminium and alkoymagnesium halides derived mainly from *exo*- and *endo*-bornan-2-ols done in the present laboratory has been given. The highlights of the contributions are as follows: (i) the development of a new class of extremely enantioselective and diastereoselective reducing reagents which are easily accessible, (ii) practical synthesis of α -deuterated benzyl alcohol, 2,2,2-trifluoro-1-phenylethanol (a chiral NMR solvent) and some aminoalcohols of physiological importance in high chemical and optical yields, (iii) a new chemical method to determine the configuration of chiral ketones and (iv) a highly satisfactory transition state model for these reactions which explains all the literature data so far.

Keywords. Asymmetric reduction; carbonyl compounds; alkoymagnesium; alkoxyaluminium halides.

1. Introduction

Asymmetric synthesis is usually defined as a reaction in which an achiral unit in a substrate molecule is converted into a chiral one under the influence of some chiral centre or centres present either in the substrate or in the reagent or in both in such a manner that one of the stereoisomers predominates. In a typically asymmetric synthesis, one of the enantiomeric product is formed in excess over the other through a kinetically controlled reaction of prochiral substrate with a chiral reagent. The free energy difference ($\Delta\Delta G^\ddagger$) between the two diastereoisomeric transition states arising out of the combination of the chiral reagent and the substrate with developing chiral centre determines the relative amount of the two enantiomers. The difference in free energy ($\Delta\Delta G^\ddagger$) is maintained by introducing appropriate steric and electronic interactions in the activated complex which is not often easy since it requires knowledge of the transition state and then the enthalpy and entropy terms of $\Delta\Delta G^\ddagger$ function may change drastically with slight change in reaction parameters.

Asymmetric synthesis is the method of choice for preparing chiral molecules of sufficient optical purity to be used subsequently in the synthesis of natural products, flavouring agents, perfumes, foods, drugs and other materials which show their beneficial effects often in one enantiomeric form. In addition to its practical utility (it avoids the tedium of resolution and saves at least half of the material), a well-planned asymmetric synthesis helps to unravel the reaction mechanism and often predicts the

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configuration of the resultant chiral molecule. Work on asymmetric organic reactions started in the beginning of the century (McKenzie 1904) but systematic studies were taken up much later. The area of asymmetric synthesis is now fast expanding and considerable amount of success has been achieved. In a few cases, chemists have engineered almost totally asymmetric synthesis thus emulating nature in her highly stereoselective enzyme reactions.

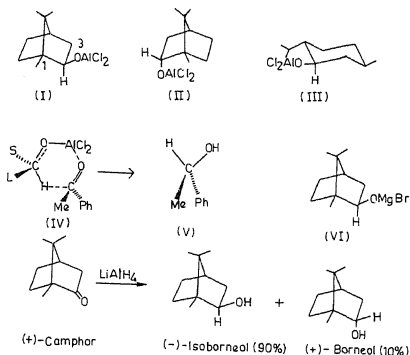
One major type of asymmetric reactions is the conversion of trigonal carbons into tetrahedral ones and the reduction of prochiral ketones to chiral alcohols falls under this category. A large variety of reagents have been used for this purpose which include modified lithium aluminium hydride, organo-metallics, organo-boranes, alkoxy-aluminium or magnesium derivatives and others all containing chiral components. Since 1966, we have been experimenting with a new class of chiral reagents which reduce different carbonyl compounds by hydride transfer. This paper records a brief account of the results of our investigations.

2. Criteria for asymmetric synthesis

Although there is no fixed guide line for asymmetric synthesis, the following criteria should be generally fulfilled for any useful asymmetric reaction: (i) The reagents must be available in high (preferably 100 %) optical purity and should be easily accessible or at least recyclisable. (ii) The chirality of the reagents should be such that it will give the desired enantiomer predominantly. In a few syntheses where a series of reactions are involved, it is possible to have either enantiomer by interchange of groups in two appropriate reagents (Meyers and Whitten 1975). (iii) The product must be easily separable from the residual chiral reagents and other side products. (iv) For the reaction to be of any practical utility, the asymmetric induction must be high (over 70 %) which means that $\Delta\Delta G^\ddagger$ in the reaction should be over 4.2 kJ/mol at ambient temperature. (v) Finally, the step leading to asymmetry should preferably be a reaction of known mechanism with an ordered transition state so that one can predict the configuration of the preponderant enantiomer. Various reactions have been developed which satisfy most of the above criteria and the readers are referred to a comprehensive treatise (Morrison and Mosher 1971), numerous reviews and monographs (ApSimon and Seguin 1979 and references 9–12 cited therein; Izumi and Tai 1977; Kagan and Fiaud 1978; Valentine and Scott 1978) which cover literature on this topic up to 1978.

3. Reagents and their preparation

Reagents used for asymmetric reduction of ketones in the present investigations, (I)–(III) are derived from chiral alcohols such as *exo*-, *endo*-bornan-2-ols (isoborneol and borneol) and *p*-menthan-3-ol (menthol), all available plentifully as cheap natural products in 100 % optical purity. Eliel and Nasipuri (1965) have shown that *sec*-alkoxyaluminium dichlorides, $RR'CHOAlCl_2$ are good reducing agents for ketones, the reduction taking place by a reversible hydride transfer similar to Meerwein-Ponndorf-Oppenauer reaction. The reduction with $RR'CHOAlCl_2$ is much faster and



alkoxyaluminium dichlorides (as III) when used in slight excess and for a short period also reduce ketones irreversibly and the reactions are thus all kinetically controlled, a necessary condition for enantioselectivity. Of the various alkoxyaluminium dichlorides, the one (I) derived from *exo*-bornan-2-ol is most efficient and has been used extensively in the present research while the others are milder and used only for specific substrates. The hydride to be transferred is attached to a chiral centre and is heavily crowded in all the reagents. This and the conformational rigidity of the ring systems ensure that the H-transfer would be highly stereoselective as indeed it is in the reduction of cyclohexanones in which predominant formation (over 90%) of the axial (the less stable) alcohols is observed (Eliel and Nasipuri 1965; Nasipuri *et al* 1976). A high degree of enantioselectivity in the reduction of proper substrates is also expected. The configurations of borneol, isoborneol and menthol are well established and the enantiomers depicted in chart 1 have (R)-configuration at α -carbon. Assuming a six-centred cyclic transition state, the predominant enantiomer is predictable from a consideration of steric interaction in the two diastereoisomeric activated complexes, the one (IV) with the two larger groups of the carbinol and of the ketone (C-1 in bornane and Ph in acetophenone) oppositely placed being preferred giving (+)-(R)-PhCHOHMe (V) from PhCOMe. Most of the criteria for a good asymmetric synthesis outlined in §2 are thus fulfilled. Along with (I)–(III), bornan-2-*exo*-yloxy-magnesium bromide (VI) (Streitweiser *et al* 1959) and a few related reagents have also been studied. Reagents (I) and (VI) have a further advantage that they are available in α -deuterated form (by reducing camphor with LiAlD_4) and may be used for D-transfer as well.

A mixture of (-)-isoborneol (90%) and (+)-borneol (10%) obtained by reduction of (+)-camphor with LiAlH_4 was used for the preparation of the reagent (I); the borneol complex being very much less reactive, its presence is ignored. No difference in stereochemical results was observed when pure isoborneol (Gerlach 1966) was used in place of the above mixture. (-)-Borneol and (-)-menthol are available commercially

and were supplied to us by Aldrich Chemical Company. The reduction was carried out either by first preparing a 'mixed hydride' solution by reacting 1 mole of LiAlH_4 with 3 moles of anhydrous AlCl_3 (Eliel 1961) and adding to it an equimolecular quantity of the chiral alcohol followed by the ketone (method A) or by preparing a solution of lithium aluminium tetra-alkoxide from LiAlH_4 and the alcohol, adding the ketone to it and finally introducing an ethereal solution of anhydrous AlCl_3 dropwise (method B). The two methods give identical results but method B is more convenient; it also allows the direct reduction product of camphor with LiAlH_4 to be used for the preparation of the reagent (I). The precise structures of the reagents are not known but they are usually formulated as alkoxyaluminium dichlorides in monomeric form. The alcohols were purified by removal of the camphoraceous impurities by steam distillation and subsequently converting them into acid phthalates without crystallising at any stage. In a few cases, preparative GC was used.

4. Results and Discussions

4.1 Asymmetric reduction of alkyl methyl ketones

A series of alkyl methyl ketones, RCOMe ($\text{R} = \text{Et}$, $i\text{-Bu}$, $i\text{-Pr}$, $t\text{-Bu}$ and cyclohexyl) was reduced with the reagent (I). The alcohols were purified by the usual combination of steam distillation, distillation, conversion into acid phthalate and regeneration. The reduction was complete but the yield of recovery seldom exceeded 50%. The results are not particularly encouraging (Nasipuri and Sarkar 1967a) but compare favourably with those reported for other reagents in this series, namely, (+)-(S)-2-methylbutylmagnesium chloride (Morrison and Mosher 1971, p. 183) and (+)-tris[(S)-2-methylbutyl]aluminium (Giacomelli *et al* 1974b). The data for all the reagents are compiled in table 1. The alcohols from reagent (I) were rich in (–)-enantiomers having (R)-configuration as expected from the transition state (IV). The extent of enantioselectivity depended on the difference in steric bulk between Me and R. Addition of anhydrous MgBr_2 in the reaction media enhanced the asymmetric induction by 40–100% (entry 2), the implication of which will be discussed later.

4.2 Asymmetric reduction of alkyl phenyl ketones

Next, a number of alkyl phenyl ketones, PhCOR ($\text{R} = \text{D}$, Me, Et, $n\text{-Pr}$, $i\text{-Pr}$, $i\text{-Bu}$, and cyclohexyl) were reduced by the reagent (I) (Nasipuri and Sarkar 1967b; Nasipuri and

Table 1. Asymmetric reduction of alkyl methyl ketones, RCOMe .

Entry	Reagents	Percent asymmetric reduction* with $\text{R} =$					Abs. confgn.
		Et	$i\text{-Bu}$	$i\text{-Pr}$	$t\text{-Bu}$	cyclohexyl	
1.	Bornan- <i>exo</i> -2-yloxy-aluminium dichloride (I)	2.8	5.7	16.4	18.0	10.0	(–)-(R)
2.	Reagent (I) + MgBr_2 (1.5 mol)	—	10.5	22.0	—	—	(–)-(R)
3.	(S)-2-Methylbutylmagnesium chloride	—	—	—	13.0	9.0	(+)-(S)
4.	Tris[(S)-2-methylbutyl]aluminium	5.3	—	16.7	19.8	—	(+)-(S)

Mukherjee 1974). In this series, the extent of asymmetric induction (10–84%) depended very much on the size of the alkyl group rising steeply in the order $D < \text{Me} < \text{Et} < n\text{-Pr} < i\text{-Bu} < i\text{-Pr}$ but decreasing again for $R = t\text{-Bu}$ and C_6H_{11} . A very similar trend has been observed when these ketones were reduced with other chiral reagents, such as (+)-(S)-2-phenylbutylmagnesium chloride (VII) (Morrison and Mosher 1971, p. 188), bornan-*exo*-2-ylmagnesium chloride (VIII) (Vavon and Angelo 1947), (+)-tris[(S)-2-methylbutyl]aluminium (IX) (Giacomelli *et al* 1973) and (+)-bis[(S)-2-methylbutyl]zinc (X) (Giacomelli *et al* 1974b) (chart 2). The results of these reductions are shown in table 2.

It may be noted that steric consideration based on cyclic transition state (IV) permits correct prediction of the absolute configuration of the predominant enantiomer in each case, but the higher asymmetric induction with increasing bulk of the alkyl groups, with phenyl still behaving as the bulkiest of all, is hard to reconcile by steric factor alone. Secondly, although phenyl, *t*-butyl and cyclohexyl groups are of comparable size, there is no parity in the extent of asymmetry induced in the three series of ketones. To cite an example, *i*-PrCOR ($R = \text{Ph}$, *t*-Bu and cyclohexyl), when reduced with (+)-(S)-2-methylbutylmagnesium chloride gave alcohols with enantiomeric excess of 24, 5 and 2% respectively (Morrison 1966). Evidently, as pointed out by Birtwistle *et al* (1964) and Cherest *et al* (1968), the origin of this discrepancy lies in some subtle electronic

CHART 2

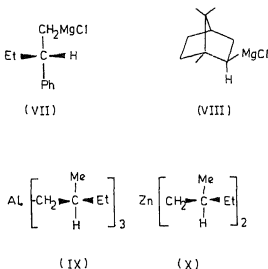


Table 2. Asymmetric reduction of alkyl phenyl ketones, PhCOR.

Enantiomeric excess for R=

Abs.

effect of the phenyl group. From practical point of view, however, the asymmetric reduction of aromatic ketones is quite satisfactory.

4.3 Asymmetric synthesis of chiral benzyl- α -d alcohol

Optically active α -deuterated primary alcohols, e.g., PhCHDOH of known configuration are important for mechanistic and biochemical studies. Several asymmetric reductions involving H- and D-transfer from chiral reagents to aldehydes are known (Streitweiser *et al* 1959; Streitweiser and Granger 1967; Althouse *et al* 1966). Six such reactions were carried out in the present laboratory (Nasipuri *et al* 1970) with reagents derived from *exo*- and *endo*-bornan-2-ols. The results are summarised in table 3 with an additional data (entry 7) from literature (Althouse *et al* 1966). α -D-benzyl alcohol, isolated in nearly 90% yield was purified by preparative GC. The interesting features in the reductions are as follows. (i) Except for reduction with the reagent (II) (entry 3), the absolute configuration of the predominant enantiomer is as expected from the cyclic transition state assuming that C-1 is effectively bulkier than C-3 in both *exo*- and *endo*-bornane derivatives. (ii) The asymmetric induction in D-transfer is appreciably higher than that in H-transfer from analogous reagents (entries 1 & 2 and 4 & 5). (iii) Bromomagnesium-derivatives of bornan-2-ols are the best enantioselective reagents (entries 4-6) bringing the highest ever asymmetric induction by chemical means. The reagents are easy to prepare and by proper combination of substrates (PhCHO and PhCDO) and reagents, either enantiomeric form may be available. The anomaly encountered with the reagent (II) regarding the configuration of the predominant enantiomer will be dealt with in a later Section. The higher asymmetric induction in D-transfer was previously ascribed to a slower rate of reaction with deuterated reagents (Althouse *et al* 1961) but it is now known that the rate factor does not significantly affect the stereochemistry of these reactions (see §4.4). The average C-H bond distance is 0.0008 Å longer than C-D and H has a larger De Broglie wavelength; hence H is able to transfer from reagent to substrate at a greater distance. The closer proximity of the two reacting centres in D-transfer produces more steric compression and more stereoselectivity (ApSimon and Seguin 1979) than in H-transfer.

Table 3. Asymmetric synthesis of PhCHDOH by alkoxymetal halides.

Entry	Reagents	Aldehyde	Enantiomeric excess (%)	Abs. confign.
1.	(-)-Bornan- <i>exo</i> -2-yloxyaluminium dichloride (I)	PhCDO	10.4	(-)-(R)
2.	(-)- α -d-Bornan- <i>exo</i> -2-yloxyaluminium dichloride	PhCHO	17.8	(+)-(S)
3.	(-)-Bornan- <i>endo</i> -2-yloxyaluminium dichloride (II)	PhCDO	32.7	(+)-(S)
4.	(-)-Bornan- <i>endo</i> -2-yloxy magnesium bromide (VI)	PhCDO	52.2	(-)-(R)
			62.5*	(-)-(R)
5.	(-)- α -d-Bornan- <i>exo</i> -2-yloxy magnesium bromide	PhCHO	64.1	(+)-(S)
6.	(-)-Bornan- <i>endo</i> -2-yloxy magnesium bromide	PhCDO	64.5	(-)-(R)
7.	(+)-2-Methyl-1-butylmagnesium chloride	PhCDO	18.1	(+)-(S)

4.4 Asymmetric reduction of some substituted phenyl ketones

To ascertain whether the rate has any influence on the stereochemistry of reduction, a number of acetophenones and phenylglyoxylic acid derivatives substituted at the para position with both electron-donating and electron-withdrawing groups were reduced by reagents (I) and (II) (Nasipuri and Ghosh 1967; Nasipuri and Mukherjee 1974). The results are summarised in table 4. The following observations are made. (i) All the acetophenones underwent reduction with remarkable consistency in asymmetric induction (25–30%) (entries 1–5) although they must have different reactivities. *p*-Methoxyacetophenone could not be reduced but ethyl phenylglyoxylate and *p*-methoxyphenylglyoxylate were reduced both by reagents (I) and (II) with almost identical asymmetric induction (entries 6 & 7 and 8 & 9). The rate of the reaction, therefore, does not have any appreciable effect on stereoselectivity—a conclusion reached by other workers also, working with Grignard reagents (Morrison and Mosher 1971, p. 202). (ii) The configuration of the predominant enantiomer in all cases except two (entries 11 and 13) was predictable from the cyclic transition state assuming that Ph behaves as a bulkier group than CO₂Et. (iii) The extent of asymmetric induction is in general low with one exception—the reduction of PhCOCO₂H with borneol-complex (II) (entry 11) in which the stereochemistry is in contravention to the normally accepted transition state. We suggest that for this slow-reacting reagent, CO₂H and possibly CN (entry 13) form some sort of complex with the reagent before the ketonic function gets reduced and thus become effectively bigger than Ph group. (iv) *p*-Nitroacetophenone was reduced smoothly and quantitatively with the reagent (I). It may be superior to sodium borohydride for the reduction of aromatic nitro-ketones which often give coloured by-products with borohydrides. (v) Finally, *p*-methoxyacetophenone remained completely inert to the reagents, possibly due to complexation with AlCl₃; conversely, the dichloroalumino-derivative of *p*-methoxyphenylcarbinol may be an

Table 4. Asymmetric reduction of substituted acetophenones and phenylglyoxylates.

Entry	Ketones	Reagents	e.e. (%)	Abs. confign.
1.	PhCOMe	(I)	25–27	(+)-(R)
2.	<i>p</i> -O ₂ NC ₆ H ₄ COMe	(I)	25 ^a	(+)-(R)
3.	<i>p</i> -ClC ₆ H ₄ COMe	(I)	28 ^b	(+)-(R)
4.	<i>p</i> -BrC ₆ H ₄ COMe	(I)	25 ^b	(+)-(R)
5.	<i>m</i> -BrC ₆ H ₄ COMe	(I)	30	(+)-(R)
6.	PhCOCO ₂ Et	(I)	14	(+)-(S) ^c
7.	<i>p</i> -MeOC ₆ H ₄ COCO ₂ Et	(I)	17	(+)-(S)
8.	PhCOCO ₂ Et	(II)	10	(+)-(S)
9.	<i>p</i> -MeOC ₆ H ₄ COCO ₂ Et	(II)	12	(+)-(S)
10.	PhCOCO ₂ H	(I)	8	(+)-(S)
11.	PhCOCO ₂ H	(II)	57	(-)-(R)
12.	PhCOCN	(I)	4	(+)-(S)
13.	PhCOCN	(II)	9	(-)-(R)

^a The alcohol was resolved through brucine salt of its acid phthalate and had α_D (max) 73.6°. ^b The optical purity of the halogenated alcohols was determined by converting them into phenylmethylcarbinol on catalytic reduction (Pd + NEt₃). ^c (+)-(S)-Mandelic acid is configurationally related to (+)-(R)-

excellent reducing agent. Some encouraging results have already been obtained (Nasipuri and Datta Gupta unpublished).

4.5 Asymmetric reduction of phenyl trifluoromethyl ketone

The dichloroalumino- and bromomagnesio-derivatives of *exo*-, *endo*-bornan-2-ols and *p*-menthan-3-ol vary considerably in their reducing property and could not be extended to include a complete series of reductions. Recently, Morrison and Ridgway (1974) have shown that phenyl trifluoromethyl ketone (PhCOCF_3) undergoes a ready and virtually irreversible Meerwein-Ponndorf-Verley-type of reduction and is thus an ideal substrate for a comparative study of stereoselectivity by this group of reagents. It was therefore reduced with dichloroalumino- and bromomagnesio-derivatives of four optically active alcohols, *e.g.*, (–)-bornan-2-*exo*-ol, (–)-bornan-2-*endo*-ol, (–)-*p*-menthan-3-ol and (+)-1-phenylethanol all having (R)-configuration at the carbinol carbon and designated for the sake of brevity as B^iOAlCl_2 (I), B^iOMgBr (VI), BOAlCl_2 (II), BOMgBr , MenOAlCl_2 (III), MenOMgBr , PeOAlCl_2 (XI) and PeOMgBr (XII) (chart 3). The results are summarised in table 5 (entries 1–10), along with some additional data from the literature. Other abbreviations in table 5 are 2MbMgCl for

CHART 3

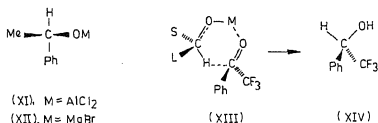


Table 5. Asymmetric reduction of PhCOCF_3 with alkoxy- and alkyl-metal halides.

Entry	Reagents	Yield (%)	e.e. (%)	Abs. confign.*
1.	(R)- B^iOAlCl_2	85	8.4	(+)-(S)
2.	(R)- $\text{B}^i\text{OAlCl}_2, \text{MgBr}_2$	65	16.1	(+)-(S)
3.	(R)- B^iOMgBr	60	2.0	(–)-(R)
4.	(R)- BOAlCl_2	85	68.0	(+)-(S)
5.	(R)- $\text{BOAlCl}_2, \text{MgBr}_2$	40	62.0	(+)-(S)
6.	(R)- BOMgBr	50	23.3	(+)-(S)
7.	(R)- MenOAlCl_2	50	77.0	(+)-(S)
8.	(R)- MenOMgBr	50	10.0	(–)-(R)
9.	(R)- PeOAlCl_2	80	4.0	(–)-(R)
10.	(R)- PeOMgBr	80	15.8	(–)-(R)
11.	(S)- 2MbMgCl	—	22.0	(+)-(S)
12.	(S)- 2PpMgCl	—	47.0	(+)-(S)
13.	(S)- $\text{Al}_2\text{Mb}, \text{OEt}_2$	—	11.6	(+)-(S)
14.	(S)- Zn_2Mb	—	5.2	(+)-(S)

* (+)-(S)-2,2,2-Trifluoro-1-phenylethanol is configurationally related to

(S)-2-methylbutylmagnesium chloride, 2PpMgCl for (S)-2-phenylpropylmagnesium chloride (Morrison and Mosher 1971, p. 191), Al2Mb for tris-[(S)-2-methylbutyl] aluminium-diethyl ether complex (IX) (Giacomelli *et al* 1975) and Zn2Mb for bis-[(S)-2-methylbutyl]zinc (X) (Giacomelli *et al* 1974a). The following general observations are made. (i) Only two of the reagents, BOAlCl₂ (II) and MenOAlCl₂ (VI) are of high enantioselectivity, affording 2,2,2-trifluoro-1-phenylethanol (XIV) with 68 and 77% enantiomeric excess respectively (entries 4 and 7) (Nasipuri and Bhattacharya 1975, 1977). This alcohol is a common chiral solvent used in NMR experiments for determining the absolute configuration and optical purity of compounds such as alcohols, amines, sulphoxides etc. (Pirkle and Beare 1969) in which it induces enantiomeric non-equivalence (Raban and Mislow 1967). The present method offers a convenient route to this alcohol of sufficient optical purity to be used directly for this purpose. (ii) Barring one or two cases (entries 3 and 8), the stereochemical results fall under two broad categories: (a) reduction with reagents derived from cyclic (R)-alcohols gives a preponderance of (+)-(S)-trifluorophenylethanol in accord with the preferred transition state (IV); (b) reduction with reagents derived from acyclic chiral components gives opposite stereochemistry, *i.e.*, (R)-alcohol from (R)-reagents and (S)-alcohol from (S)-reagents (entries 8–14). The preferred transition state for cases under (b) appears to be the one (XIII) in which Ph and L are on the same side of the ring, *i.e.*, CF₃ behaves as bulkier than Ph. This will be discussed in §6. (iii) The addition of MgBr₂ (Lewis acid) increases the stereoselectivity in one case (entry 2) almost by 100%.

4.6 Asymmetric reduction of aminoketones

A few aminoketones (XV)–(XXIII) (chart 4) were reduced with the reagent (I) (Samaddar *et al* 1983). The aminoalcohols were readily separable because of their acid-solubility and obtained in high chemical yields (table 6). Some of them are physiologically active and their availability in optically pure form is desirable. Tomina *et al* (1972) and Andrisano *et al* (1973) reduced a number of these ketones using chiral organomagnesium reagents and LiAlH₄ modified by (–)-menthol respectively. The easy accessibility of our reagent, the predictability of the product configuration and high optical yield make the present method a practical one. The three acetylpyridines (XXI)–(XXIII) were reduced to 1-(2-, 3-, and 4-pyridyl)ethanols but the asymmetric induction was low.

Chart 4

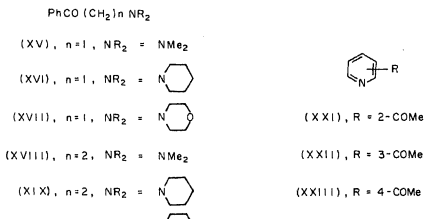


Table 6. Asymmetric reduction of aminoketones (XV)–(XXIII).

Entry	Aminoketone	Yield (%)	e.e. (%)	Abs. confign ^a .
1.	(XV)	78.0	66.7	(+)-(S)
2.	(XVI)	90.5	60.0	(+)-(S)
3.	(XVII)	81.5	71.0	(+)-(S)
4.	(XVIII)	82.0	65.0	(+)-(R)
5.	(XIX)	84.5	58.0	(+)-(R)
6.	(XX)	77.5	92.0	(+)-(R)
7.	(XXI)	75.0	11.5	(+)-(R)
8.	(XXII)	60.0	37.0	(+)-(R)
9.	(XXIII)	70.0	14.7	(+)-(R)

^a (S)-Configuration of XV–XVII are related to (R)-configuration of XVIII–XXIII.

4.7 Asymmetric reduction of miscellaneous ketones

Benzyl methyl ketone on reduction with the reagent (I) afforded benzylmethylcarbinol in 50% yield with $\alpha_D-3.1^\circ$ corresponding to 11.5% of enantiomeric excess (Nasipuri and Datta Gupta Unpublished). β -Tetralone although reduced smoothly did not give optically active alcohol. α -Tetralone, α -hydrindone and fluorenone were not reduced at all. Dichloroaluminoderivative of 9-fluorenol proved to be a very good reducing agent for cyclic ketones (Nasipuri and Datta Gupta Unpublished).

4.8 Stereoselective reduction of triterpenoid ketones

A number of 3-oxotriterpenoids and 3-oxosteroids such as α -amyrone, lupenarborinone, methyl ursonate, methyl oleanonate, friedelin, cholestan-3-one and dimethylcholestan-3-one were reduced by the reagent (I). In all cases, axial alcohols were obtained predominantly (75–100%) (Nasipuri *et al* 1976). In the wider sense of the term, this may also be regarded as asymmetric synthesis or more specifically diastereoselective synthesis. In most cases, a single crystallisation of the epimeric mixture afforded the pure axial alcohol.

5. Kinetic resolution of exo- and endo-bornan-2-ols

Four chiral ketones, namely, (+)-(R)-3-methylcyclohexanone (XXIV), (–)-1(R), 4(R)-p-menthan-3-one (XXV), (+)-1(S), 4(R)-fenchone (XXVI) (Chart 5) and 5- α -cholestan-3-one all of known configuration were treated with 2 moles of dichloroaluminum complexes of ($\pm$)-exo- and ($\pm$)-endo bornan-2-ols (Nasipuri and Mukherjee 1976). Camphor formed was uniformly (+)-rotatory isolated as alkali-soluble (–)-rotatory oxime (table 7). Evidently, (–)-exo-bornan-2-yloxyaluminum dichloride (I) was consumed faster than its antipode and the transition state (XXVII) must be favored over its diastereoisomer. The reagent attacks the ketones from the less hindered (equatorial or β) (see §4.8) as shown in XXVII and steric interactions arise due to substituents which are only on the upper side (β) of the ring. Any substituent below the plane of the ring (α) such as Pr^i in menthone or more than two carbon atoms away from

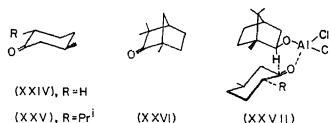


Table 7. Kinetic resolution of camphor by oxidation of bornan-2-ols.

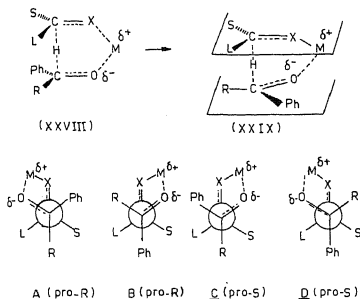
Entry	Ketone	Camphor-oxime from (±)-exo-isomer		Camphor-oxime from (±)-endo-isomer	
		α_D	e.e. (%)	α_D	e.e. (%)
1.	(+)-3-Methylcyclohexanone (XXIV)	-3.1°	7.3	+0.36°	1.0
2.	(-)-Menthone (XXV)	-37.8°	89.0	+6.48°	15.3
3.	(+)-Fenchone (XXVI)	-29.55°	70.0	—	—
4.	3-Cholestanone	-3.8°	9.0	+0.42°	1.1

C=O as 10-Me in 3-cholestanone will have no appreciable steric effect. Thus for 3-methylcyclohexanone (XXIV) and menthone (XXV), it is only the equatorial β -Me that matters and it is better off being on the side away from C-1-Me of bornane moiety. This puts XXIV and XXV on a similar footing both of them consuming (-)-exo-bornan-2-ol at a faster rate, menthone more so perhaps due to its rigid molecular frame (see also Morrison *et al* 1969). It thus constitutes a convenient chemical method for the determination of configuration of chiral ketones.

6. A new transition state model

During the discussion of the results, we made certain observations which did not fit in the cyclic transition state (IV). These include (i) high asymmetric induction when a Ph group is attached to C=O or is a part of the reagent or both; (ii) enhanced enantioselectivity in the reduction of PhCOR as the bulk of R increases; (iii) atypical enantiomer formed in reduction of PhCOCF₃ with acyclic chiral reagents; and (iv) anomalous behaviour of bornan-endo-2-yloxyaluminium dichloride (II) during reduction of PhCDO. We suggested a transition state model for these reductions (Nasipuri *et al* 1967) to explain observation (ii) primarily based on the effect of rate on stereochemistry which subsequently proved to be wrong (see §4.4). Recently, we have advanced a new transition state model (Nasipuri *et al* 1971) which as we shall see in the sequel explains all the discrepancies and has been accepted and used by other workers in this field (Giacomelli *et al* 1973; Cabaret and Welvert 1974; ApSimon and Seguin 1979). The metal in the reagent first coordinates with C=O which is followed by an energetically preferred linear H-transfer. The complex (XXVIII) (chart 6) twists along C...H...C axis to relieve steric and torsional strain, with the two oppositely developing dipoles, O⁻ and XM⁺ (M stands for Al, Mg and Zn, and X for O and CH₂)

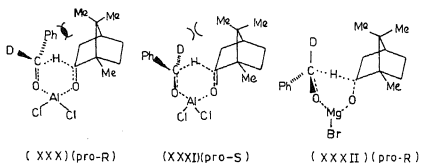
CHART 6



loosely bound in space as shown in structure (XXIX) for (R)-reagents. The steric interactions in the reactive conformations may be appraised in Newman-type formulae viewed along C...H...C bond, the relatively short C-H bond and the radial distribution of the groups largely compensating for the extra H sandwiched between carbons (Nasipuri and Mukherjee 1974). Four such structures A, B, C and D (chart 6) may be envisaged the first two leading to (R)-alcohol and the last two to (S)-alcohol. Between A and B, A is favoured both sterically (L and Ph anti) and electronically (XM⁺ flanked by two negative dipoles, O⁻ and Ph), while between C and D, C is favoured on similar grounds. The product ratio, R/S will, therefore, depend mainly on the relative stability of A (pro-R) and C (pro-S). Simple steric consideration (Ph ↔ S + L ↔ O⁻ in A and Ph ↔ L + S ↔ O⁻ in C) shows that A is more stable and so (R)-alcohol predominates. As R increases in bulk, a buttressing effect operates, rotation to separate L and R in C will push Ph against L whereas a similar rotation in A is easy. This explains the puzzling fact of increased asymmetric induction with increasing size of R in PhCOR. To put it in a different language, the increased steric hindrance due to bulkier R prevents the conformational mobility of all the groups being compressed but more so in C than in A (Giacomelli *et al* 1973). Conformational analysis of B (pro-R) and D (pro-S) shows that D is more stable (L ↔ R + S ↔ O⁻ in B and S ↔ R + L ↔ O⁻ in D) and hence their involvement will reduce the stereoselectivity. This is exactly what happens in the reduction of aliphatic ketones which lacks the electronic effect of Ph and the participation of A and C lessens.

For reduction of PhCOCF₃ (R = CF₃ in A-D), the reactive conformers in which XM⁺ lies between -O⁻ and CF₃ (i.e., B and D) should determine the steric course since CF₃ is a stronger (-) dipole than Ph, and D being more stable, the enantioselectivity will be reversed. For cyclic reagents (L and S joining to form a ring),

CHART 7



linkage. Thus OAlCl_2 being a stronger electrophile than OMgBr , is drawn nearer to $-\text{O}^-$ leading more or less to the classical cyclic transition state shown in figure (XXX) (chart 7) for reaction of PhCDO with $(-)\text{-BOAlCl}_2$ (II). In this conformation, one of the overhanging 9-Me interacts strongly with Ph and so the other transition state (XXXI) with Ph on the same side as C-1 is preferred. With $(-)\text{-BOMgBr}$, on the other hand, the preferred conformation is XXXII with Mg loosely bound to $-\text{O}^-$. Thus the differential behaviour of BOAlCl_2 and BOMgBr is also explained. For ROAlCl_2 reagents, it is probable that the transition state (XXIX) leans more towards semi chair conformation with non-linear $\text{C} \dots \text{H} \dots \text{C}$ bond in which the steric interactions are eased out so that asymmetric induction is low (e.g., PhCDO reduction, table 3). But when both the carbinol and ketone bear heavy substituents, the quasi chair conformation changes over to the linear one (XXIX) to avoid 1,3-diaxial interaction and the asymmetric induction goes up. This is borne out by the observation that when anhydrous MgBr_2 is added in the reaction media, asymmetric induction increases due to weakening of the coordinating bond (Gould 1964).

7. Conclusion

The present investigation has provided a few highly enantioselective and diastereoselective reducing agents. Because of their easy accessibility, they will prove very useful in organic synthesis. A highly satisfactory and generally accepted transition state model for these reductions has also been postulated.

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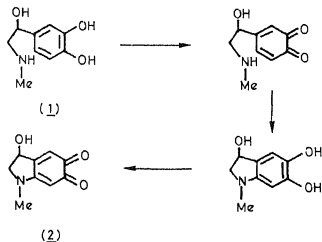
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Quinone-imines and their derivatives as transient intermediates in cyclisation reactions¹

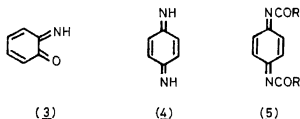
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It has long been recognised that quinones may be intermediates in several cyclisation reactions (Wanzlick 1968). The ring-closure in such reactions is brought about by an intramolecular Michael addition of a suitable nucleophile located in the side chain emanating from one of the carbon atoms of the quinone. An example is the formation of adrenochrome (2) from epinephrine (1) (scheme 1). Here, the intermediate *o*-quinone, generated *in situ*, undergoes intramolecular Michael addition, followed by a further oxidation to form adrenochrome (2). Intramolecular addition of an amine to the carbonyl group of a *p*-benzoquinone intermediate may be one of the crucial steps in the Nenitzescu synthesis of 5-hydroxyindoles (Allen 1973).



Scheme 1

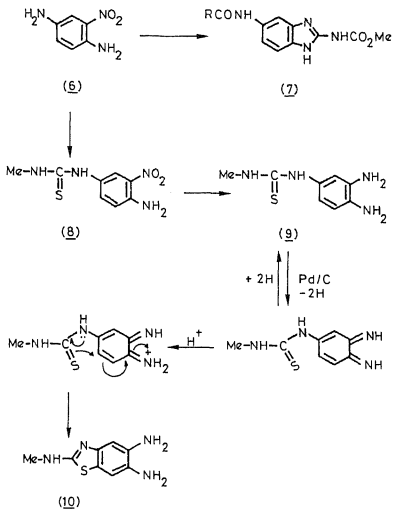


Oxidation of an *o*-aminophenol would give a quinone-monoimine (3); in such systems, it has been well-established that the first addition takes place to the $C=C-C=N$ group. Subsequently a second nucleophile can add intramolecularly to the $C=C-C=O$ generated by a further oxidation. Such processes have been extensively investigated in the context of actinomycins and ommochromes (Wanzlick 1968).

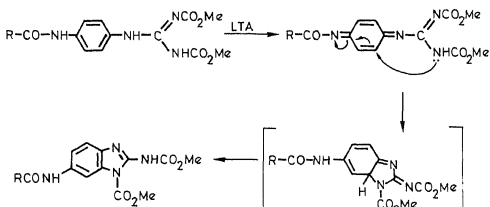
Quinone-diimines such as (4) are extremely reactive species and undergo very easy reaction with nucleophiles (Finley and Tong 1970). The disadvantage with quinone-diimines is their extreme instability. The pioneering work of Adams and his group has established that quinone-imides (5) are excellent substrates for addition reactions by virtue of their ease of preparation and relative stability compared to the quinone-diimines (Adams and Reifschneider 1958). However, intramolecular examples of addition to quinone-diimines or quinone-imides seem to be unknown.

Our entry into the area of intramolecular nucleophilic addition to quinone-diimines and quinone-imides came about partly through serendipity. A few years back, we were interested in the synthesis of derivatives of 5-amino-benzimidazole-2-carbamates (7). We achieved this by selective functionalisation of the amine *meta* to the nitro group in 2-nitro-*p*-phenylene diamine (6), followed by reduction and cyclisation (Rajappa and Sreenivasan 1980a). The functionality in these examples was an amide, urea or urethane (*R* in 7 was alkyl, aryl, alkylamino or alkoxy). When the functional group was a thiourea, however, the reduction step provided an unexpected result. Catalytic reduction in neutral solution (10% Pd-C, methanol, 29°, 1 atm. pressure) of the 4-thioureido-2-nitroaniline (8) gave both the expected diamine (9) and the cyclised product (10). The structure of the latter was proved by its mass spectrum (MW 194) and 1H NMR spectrum (two singlets in the aromatic region). Catalytic reduction of 8 in acid solution gave only the hydrochloride of 5,6-diamino-2-methylaminobenzthiazole (10). The thioureidophenylene diamine (9) could be converted to the benzthiazole (10) by stirring in ethanolic HCl with Pd/C catalyst in the presence of atmospheric oxygen. Omission of the catalyst resulted in recovery of 9 as its hydrochloride. These results led to the postulation of the following mechanism (Rajappa and Sreenivasan 1980b). In neutral solution, in the presence of catalyst, an oxidation-reduction equilibrium is set up between 9 and the corresponding quinone-diimine. Protonation of the latter leads to a rapid, irreversible cyclisation, with the ideally located sulphur atom acting as the nucleophile. A subsequent prototropic shift results in the formation of the benzthiazole (10) (scheme 2).

This chance encounter with a presumed transient quinone-diimine set us wondering about the possible use of such intramolecular nucleophilic attack on deliberately generated quinone-imides as a route to the synthesis of novel heterocycles. We anticipated the following difficulty: quinone-imides are normally made by lead tetraacetate (LTA) oxidation of 1,4-*bis* acylaminobenzene derivatives. The prospective side-chain nucleophile should be stable under these conditions, and yet be reactive enough to attack the newly formed quinone-imide before the latter embarked on other unwanted reaction pathways. The nucleophile-bearing side-chain can be attached either to a carbon atom of the quinone-imide as in the case of the quinones mentioned earlier, or to one of the nitrogen atoms of the potential quinone-imide system. In the latter event, it should also serve the function of a stabilising group on the quinone-imine, i.e., it should be a surrogate for the acylamine normally employed as substrates in



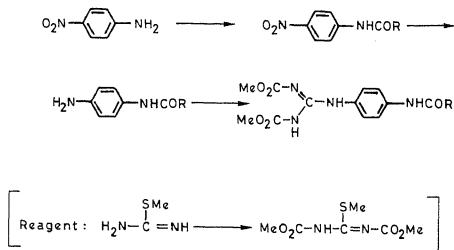
Scheme 2



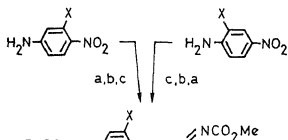
an N',N''-biscarbomethoxy-N-(4-acylamino) phenylguanidine; LTA oxidation of this would hopefully produce the corresponding quinone-imide derivative in which either of the nitrogen atoms bearing a carbomethoxy group would be poised to attack the C=C-C=N system. The product after cyclisation would be a 6-acylamino-1-carbomethoxybenzimidazole-2-carbamate.

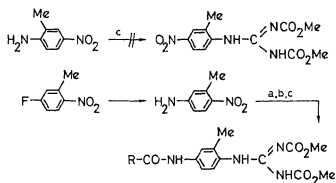
The precursor itself could be easily synthesised from 4-nitroaniline by acylation and reduction, followed by reaction with N,N'-biscarbomethoxy-S-methyl thiourea (scheme 4). Similar 4-acylamino phenyl guanidines with an extra substituent at either position 2 or 3 of the benzene ring have also been prepared. The synthetic route adopted depends upon the availability of the starting materials. If the substituent were to be at position 2 (adjacent to the guanidine), then in principle, either of the two sequences shown in scheme 5 can be used. In practice, however, it turned out that an NH₂ *para* to NO₂ does not react with the reagent (step 'c'). Hence the alternate route shown in scheme 6 had to be used.

Substrates with the substituent (Me, OMe or Cl) adjacent to the acylamino group could be easily prepared from the corresponding readily available *p*-nitroanilines.



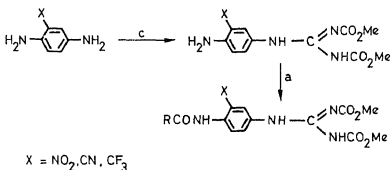
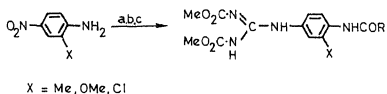
Scheme 4





Scheme 6

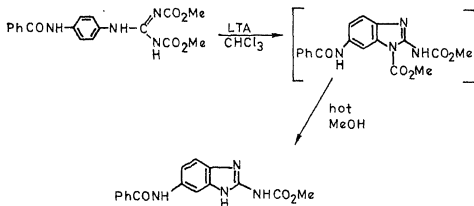
However, if the substituent was strongly electron-withdrawing (NO_2 , CN , CF_3), the best route was to start from the corresponding *p*-phenylene diamine as shown in Scheme 7. Initial reaction with the reagent (step 'c') took place exclusively on the NH_2 *meta* to the deactivating substituent; subsequent acylation gave the required 4-acylamino-3-substituted-phenylguanidine.



Scheme 7

We now turn to the results of oxidative cyclisation of the various substrates discussed above.

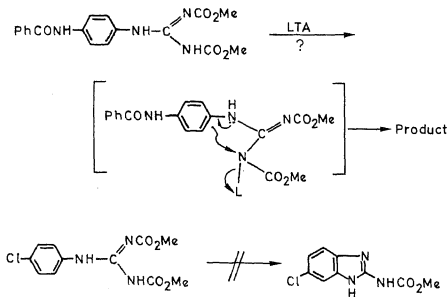
The simple 4-benzamidophenylguanidine was treated with LTA in refluxing chloroform. After filtering off the lead salts, the chloroform was evaporated and the product isolated. The compound at this stage appeared to be the required one; but it was still contaminated with small quantities of lead salts. In order to remove these, it was digested for a few minutes in boiling methanol and filtered. This procedure removed the lead salts; but at the same time, it also achieved 1-decarbomethoxylation! So the final



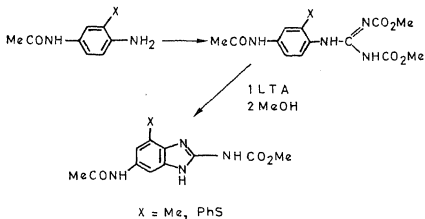
Scheme 8

That 6-acylamino-1-carbomethoxybenzimidazole-2-carbamates are indeed the initial cyclisation products in such LTA oxidation reactions, was established by determining the ^1H NMR spectra of the compounds before treatment with methanol. Thus the 6-acetamido derivative showed the presence of two distinct OMe groups (3.89, 4.17 ppm in CDCl_3) at this stage; the benzimidazole obtained on methanolysis of this compound has only one OMe group (4.07 ppm in TFA).

We have assumed in the above discussion that the cyclisation proceeds *via* a quinone-imide. However, an alternate mechanism would involve nucleophilic attack by the *ortho*-carbon on the nitrogen atom which now carries a leaving group L [this could be $\text{Pb}(\text{OAc})_3$ or OAc] (scheme 9). However, N',N'' -biscarbomethoxy- N -(4-chlorophenyl)guanidine was recovered unchanged after treatment with LTA under the above conditions. It is clear therefore that a *p*-acylamino group is necessary for the cyclisation; this strongly implicates the intermediacy of a quinone-imide. Further confirmation of this is provided by the substituent effect on the site of cyclisation as discussed below.

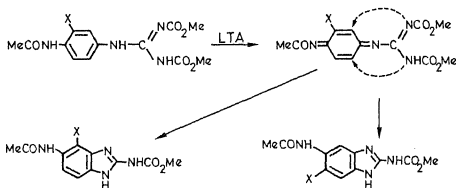


In scheme 6 we had illustrated the preparation of 4-acylamino phenylguanidines with a methyl group adjacent to the guanidine. In such compounds there is only one *ortho*-position available for cyclisation and so there is no ambiguity. The resulting benzimidazoles have the substituent at position 7 and the acylamino group at position 5 (scheme 10).



Scheme 10

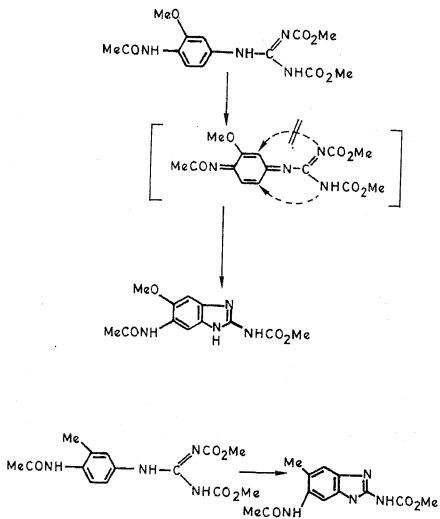
On the other hand, if the substituent is next to the acetamide, the guanidine has both *ortho*-positions free; attack by the nucleophile can take place in either direction (scheme 11). The two possible isomers can be distinguished by ^1H NMR (two singlets *vs* an AB quartet in the aromatic region).



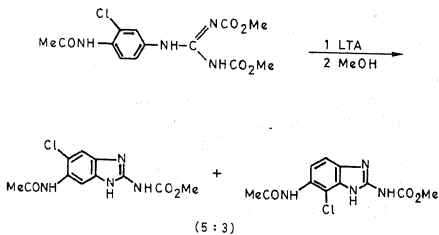
Scheme 11

Consider the LTA oxidation of the 3-methoxy-4-acetamidophenylguanidine (scheme 12). Of the two possible loci for nucleophilic addition in the quinone-imide, the enol-ether terminus is electron-rich. Addition therefore is expected to take place at the other locus. This is exactly what happens in practice. Only one isomer is formed in 24% yield (^1H NMR in TFA: singlets at 7.33 and 8.50 ppm). The other isomer, if present, is below the detectable limit. A similar situation prevails with the methyl substituent.

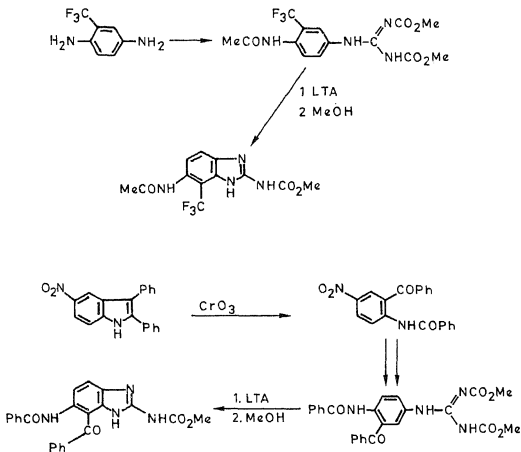
When the substituent is chlorine, its ($-I + M$) effect comes into operation and so



Scheme 12



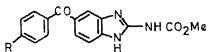
Our hypothesis that the regioselectivity of these cyclisations is largely controlled by the electronic factors associated with the substituent can be considered proven only if the sterically disfavoured vicinal cyclisation takes place exclusively when the substituent is electron-withdrawing. For this purpose, the CF_3 substituted derivative was ideal. To our delight, LTA oxidation of this gave exclusively the vicinal cyclised product (yield 20%) as shown by the AB quartet in the ^1H NMR spectrum at 7.70 and 8.03 ppm. The carbonyl substituent exerts a similar effect as shown by the oxidative cyclisation of the phenyl ketone (scheme 14).



Scheme 14

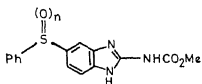
More powerful electron-attracting groups like NO_2 or CN deplete the nucleus of so much of its electron-density that the oxidation step itself fails; the substrates are recovered. At the other extreme, when there is an excess of electron-release into the ring, oxidative polymerisation predominates; quinone-imine intermediates thus fail to yield cyclised products in contrast to quinone-imides. However, within the range of substituents discussed above, a wide variety of substrates undergo the regioselective oxidative cyclisation. The position *para* to the guanidine can be occupied by an NHCOR , NHCO_2R , NHSO_2R or NHSO_2NR_2 . Further a $\text{C}=\text{C}$ or $\text{C}=\text{N}$ can be interposed in some cases between the CO or SO_2 and the NH at that position.

Apart from the chemical novelty of the synthesis we have described above, it has also great relevance to our quest for more efficient drugs against parasitic diseases. Benzimidazole-2-carbamates with specific substituents at the 5-position are known to be active against hookworms and roundworms (scheme 15). These are invariably



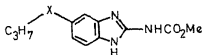
R = H : Mebendazole

R = F : Flubendazole



n = 0 : Fenbendazole

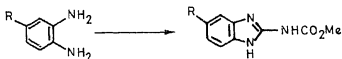
n = 1 : Oxfendazole



X = O : Oxibendazole

X = S : Albendazole

Synthesis:



Scheme 15

synthesised from an appropriately substituted *o*-phenylenediamine. The route we have described above opens up the possibility of preparing benzimidazole-2-carbamates with novel substitution patterns, inaccessible by conventional methods.

The oxidative cyclisation to benzimidazole-2-carbamates was first disclosed at the 48th Annual General Meeting of the Indian Academy of Sciences at Nainital on 10 October, 1982. A preliminary communication has subsequently been published (Rajappa *et al* 1983). It is appropriate that the present elaboration of the theme should find a place in the Golden Jubilee Issue of the Proceedings of the Academy.

The author wishes to thank his colleagues, Mr R Sreenivasan and Miss A V Rane for their excellent contribution to the work reported here.

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Mechanism of aromatic lithiation reactions—Importance of steric factors

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Abstract. N,N-Dimethyl-1-naphthylamine and N,N-dimethyl-2-aminobiphenyl do not undergo *ortho*-lithiation although lithiation at a distant, but sterically close, position does occur. The result, although apparently anomalous, can be explained by Roberts-Curtin mechanism, taking into consideration the steric strain present at the transition state corresponding to the proton abstraction process.

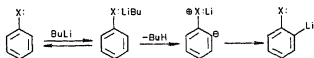
Keywords. Aromatic lithiation; Roberts-Curtin mechanism; N,N-dimethyl-1-naphthylamine; N,N-dimethyl-2-aminobiphenyl; Steric factors; Transition state.

Compounds like anisole, N-methylbenzamide, N,N-dimethylbenzylamine etc which carry functional groups bearing heteroatoms with unshared electron pair are readily lithiated, specifically at *ortho* position, on treatment with *n*-BuLi in ether or hexane (Gschwend and Rodriguez 1979). Under these conditions benzene itself is not lithiated to any significant extent†. In recent times these heteroatom-directed aromatic lithiation reactions have been extensively used for the synthesis of several condensed heterocyclic compounds (Narasimhan and Mali 1983).

The intimate mechanism of this important reaction is as yet not fully established. There are indeed difficulties in this regard (Mallan and Bebb 1969). In the first instance, the nature of the lithiating species, RLi, as present in the reaction medium, is not known. Li exists in different polymeric states in different solvents. However, it is very likely that monomeric RLi, although in only small concentration, is also present, in equilibrium with the oligomers, in the reaction medium. Is it the polymeric RLi or the monomeric (presumably more reactive) species which is the lithiating agent? In most of the lithiation reactions, lithium salts (*e.g.* LiBr) are also present in the reaction medium. What is the influence of these on the mechanism of the reaction, particularly on the nature and reactivity of the lithiating species? Finally what is the role of the solvent on the stability of the lithiating species, the transition state and the final organolithium compound formed in the reaction?

Remarkably, however, aromatic lithiation reactions show a large regioselectivity (Gschwend and Rodriguez 1979), as in the exclusive *ortho*-lithiation of anisole, N-methylbenzamide, N,N-dimethylbenzylamine etc.

A widely accepted mechanism, which explains *ortho* lithiation, is due to Roberts and Curtin (1946). This is shown in scheme 1. In this, the first step is the reversible



Scheme 1



Scheme 2

complexation of the RLi reagent with the electron donor atom present on the substituent in the aromatic ring. In the second step, which is rate determining, the *complexed* RLi abstracts the sterically close *ortho* hydrogen as a proton, presumably by a collinear attack from the back side of the hydrogen in the C-H bond*. This step, in which R is converted to RH, is expected to be irreversible when *n*-BuLi or PhLi is the lithiating agent and hence would be under kinetic control†. The last step is the shift of the lithium atom from oxygen to the *ortho* carbon atom. The organolithium compound would be, presumably, stabilised by internal coordination‡.

Where there is a possibility of the lithiation reaction occurring at more than one position in the aromatic substrate, as in the case of 1,3-dimethoxybenzene or 1- and 2-methoxynaphthalenes, it is possible to visualise a scheme in which the different organolithium species formed are under equilibrium control. (Scheme 2)

Equilibration of the aromatic lithium species was indeed suggested for the lithiation of 1-methoxynaphthalene (Barnes and Nehmsmann 1962), where it was stated that the initial product was the 8-lithio compound, which then isomerised to the 2-lithio compound. This experiment has been disputed and it is now well established that the 2-lithio compound is directly formed and not *via* the 8-lithio compound (Graybill and Shirley 1966).

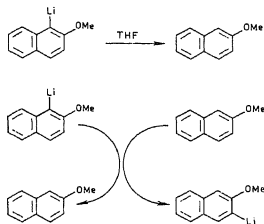
Recently Cram and coworkers (Wilson and Cram 1982) have reported another experiment in which there is an *apparent* isomerisation of 1-lithio-2-methoxynaphthalene. Thus when 1-lithio-2-methoxynaphthalene, generated from 1-bromo-2-methoxynaphthalene by treatment with *n*-BuLi in THF, was reacted with an electrophile, the products formed corresponded to reaction at 1- and also at 3-positions in the naphthalene ring, the latter predominating. Obviously 3-lithio-2-methoxynaphthalene is also formed in this reaction. The formation of 3-lithio-2-methoxynaphthalene, however, is not an isomerisation reaction. It is formed by an alternate mechanism, as shown in scheme 3 (Wilson and Cram 1982), in which, in the first instance, 1-lithio-2-methoxynaphthalene reacts with the solvent to produce 2-methoxynaphthalene and the latter is further lithiated by 1-lithio-2-methoxynaphthalene.

* To the extent collinear approach is not possible, the energy of the proton abstraction process will be larger.

† Indeed, the products BuH and PhH (pK_a 45–50 and 35–37 respectively) cannot be lithiated under the experimental conditions. Substituted benzenes, such as anisole, *N*-methylbenzamides would have lower pK_a value for the *ortho* hydrogen.

‡ An alternate mechanism was proposed for the lithiation reaction a few years back (Shirley and Hendrix

1968). This involved intermediacy of radical ions and the species . This mechanism has since been



Scheme 3

The mechanism is in agreement with the well-known fact that organolithium compounds are less stable in THF and 2-methoxynaphthalene is lithiated predominantly to give the 3-lithio compound.

The above observation, however, is not general. Literature abounds with examples where organolithium compounds, obtained *via* halogen-metal exchange, do not isomerise. Indeed, for this reason, organolithium compounds, obtained this way, have been extensively used in organic synthesis. Specifically now we find that when 1-lithio-2-methoxynaphthalene, obtained from 1-bromo-2-methoxynaphthalene by treatment with *n*-BuLi in *ether* solvent, is treated with dimethylformamide (DMF), no product corresponding to substitution at 3-position is obtained. In this reaction, thus, no 3-lithio compound was formed in the reaction mixture *i.e.* no isomerisation had occurred. Again, when 1-lithio-2-methoxynaphthalene, as obtained above in *ether* solution, was treated with 2-methoxynaphthalene, no 3-lithio compound was obtained (as evidenced by further reaction with DMF). The latter experiment indicated that, in *ether* solution 1-lithio-2-methoxynaphthalene cannot lithiate 2-methoxynaphthalene.

In similar experiments it was found that 4-lithio-1,3-dimethoxybenzene, obtained by treatment of 4-bromo-1,3-dimethoxybenzene with *n*-BuLi in *ether*, did not isomerise to 3-lithio-1,3-dimethoxybenzene, as evidenced by further reaction with benzophenone, although the latter was expected to be thermodynamically the more stable. And also, 4-lithio-1,3-dimethoxybenzene did not lithiate 1,3-dimethoxybenzene.

The above experiments* indicate that organolithium compounds, once formed, do not undergo any isomerisation *at least in ether solution*. Their formation, then, is under kinetic control.

The other observed orientation (Gschwend and Rodriguez 1979) in aromatic lithiation reactions are in accord with the mechanism of lithiation reaction given above. Thus,

(i) lithiation occurs not only at the *ortho* position, but also at other sterically close positions (scheme 4). This is to be expected, for the RLi reagent, complexed to the

* Several lithiation reactions have been repeated in our laboratory to have uniform experimental conditions



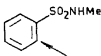
Scheme 4



Scheme 5



Scheme 6



Scheme 7



electron donor atom on the substituent, can abstract hydrogen atoms also from other positions, provided they are sterically accessible to it;

(ii) lithiation occurs even when the heteroatom is not directly attached to be aromatic ring, but is one or two atoms away (scheme 5). The RLi reagent would still complex with the electron donor atom and the transition state corresponding to proton abstraction can be readily formed. However, when the number of intervening atoms is more than two, there will be difficulty in achieving the transition state;

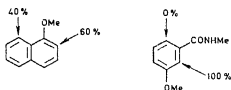
(iii) lithiation occurs at the *ortho* or other sterically close positions even when the lithiation directing group, as a whole, is electron withdrawing, provided it still carries an electron donor atom with which the RLi reagent can complex (scheme 6). Interestingly, such groups, which are meta-orienting in acid catalysed electrophilic substitution reactions, are found to be better *ortho* lithiation-directing. It may be noted that some of these groups, *e.g.* $-\text{CONHCH}_3$, would have negative charge on them on treatment with the RLi reagents. Presumably, despite the negative charge, the electron-withdrawing ability of such groups is substantial, which then leads to increased acidity of the *ortho* hydrogen atom*, a condition favourable for the aromatic lithiation reaction;

(iv) when more than one lithiation directing group is present, lithiation is directed by that group which complexes better with the RLi reagent (scheme 7);

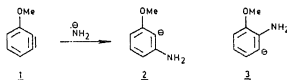
(v) when more than one position for lithiation is present, lithiation occurs predominantly at that position which carries the more acidic hydrogen atom from among those which are *ortho* or sterically close with respect to the better complexing group (scheme 8).

It may be noted here that the acidity to be considered, in these reactions, where *n*-BuLi is the lithiating agent, is the kinetic acidity. This is because, in the rate-determining step, the proton abstraction itself is under kinetic control. Further, in these cases (aromatic lithiations), the acidity of the hydrogen is determined essentially by the inductive effect and not, to any significant extent, by the resonance effect†. The

* It may be noted that dianions are readily formed from CH_3CONHR in contrast to, for example, even



Scheme 8



Scheme 9

situation is similar to the formation of similar types of species when substituted benzyne react with strong bases such as NH_2^- . The benzyne **1**, for example, reacts with NH_2^- to give **2** rather than **3** (March 1977) (scheme 9). Had the resonance factors been important, the negative charge on the species **2** would have been destabilised by the methoxyl group at the *ortho* position.

In summary it may be stated that complexation and acidity of the hydrogen atom *ortho* or sterically close to the complexing group are the two important factors which govern orientation in aromatic lithiation reactions. Complexation is more important. Thus, *p*-methoxy-*N,N*-dimethylbenzylamine is lithiated at *ortho* position with respect to the dimethylaminomethyl group despite the fact that the hydrogen atom *ortho* to this group is less acidic than that *ortho* to the methoxyl group (Gschwend and Rodriguez 1979).

Steric factors in aromatic lithiation reactions

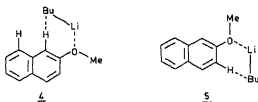
Steric factors, evidently, would be also important in lithiation reactions. Steric factors can come into play at three stages: (i) complexation of RLi with the electron-donor group, (ii) attainment of the transition state leading to lithiation and (iii) reaction of the organolithium compound with the electrophilic reagent. The influence of the steric factors on the first and the last stages, however, would be on the rate rather than on the orientation*. The orientation in aromatic lithiation is then essentially governed by the steric factors in the transition state.

The role of steric factors on orientation in lithiation reactions can be seen in the lithiation of 2-methoxynaphthalene. Here there are two alternate *ortho* positions, 1 and 3, for lithiation. The hydrogen at 1-position would be more acidic since the double bond at the 1(2) position would transmit the inductive effect of the oxygen function better to this than to 3-position. Lithiation is then expected to occur at 1-position. Experimentally, however, lithiation occurs predominantly at 3-position.

The above observation can be rationalised on the basis of the steric strain in the transition states, corresponding to lithiation at 1- and 3-positions. These transition states are shown in scheme 10. In both the transition states a linear approach of the Bu to H-C bond is assumed, since this would be the most favoured pathway for the reaction.

It may be now noted that, of the two transition states **4** and **5**, **4** would be more

* Complexation can influence orientation in the sense that lithiation will occur *ortho* or sterically close to that group which complexes better with the lithiating agent. This aspect has already been referred to.



Scheme 10



Scheme 11

strained due to steric repulsion between the hydrogen at 8-position and the butyl group. The lithiation reaction would be then favoured *via* the transition state 5 and would occur predominantly at 3-position.

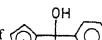
Gilman and Sunthakar (1981) had explained the preferential lithiation of 2-methoxynaphthalene at 3-position invoking resonance factors. According to this, the methoxyl group would increase the electron density (presumably π -electron density) at 1-position, which in turn would decrease the acidity of the hydrogen at that position. The hydrogen at 3-position would be then relatively more acidic, leading to lithiation there. It has already been pointed out that π -electron density is not important for the acidity of the aromatic hydrogen*.

Apparently anomalous lithiation reactions

There are certain lithiation reactions which apparently do not fit in the above scheme of mechanism. Thus 1-naphthol and 2-aminobiphenyl are lithiated exclusively at 8- and 2'-position respectively (scheme 11). In the above, one would have expected lithiation to occur at 2- and 3-positions respectively, since these positions, having an oxygen or nitrogen at the adjacent position, would carry the more acidic hydrogen. A closer examination, however, would indicate that this is not so. The first event that occurs when the above compounds are treated with RLi reagent would be formation of ArO^- and ArNH^- species (or corresponding ion pairs ArOLi , ArNHLi). Aromatic lithiation actually occurs on these species. Now, in these species, the negative charge on the oxygen or nitrogen would indeed decrease the acidity of the hydrogen at the adjacent (*ortho*) position, while those at the distant 8- and 2'-position would be relatively unaffected. The latter would be relatively more acidic and hence lithiation would be more favoured at these positions. The observed orientation in the lithiation of 1-hydroxynaphthalene and 2-aminobiphenyl, thus, is not anomalous but is in agreement with the Roberts–Curtin mechanism.

Lithiation of N,N-dimethyl-1-naphthylamine and N,N-dimethyl-2-aminobiphenyl

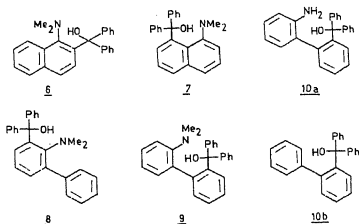
On the basis of Roberts–Curtin mechanism, lithiation of N,N-dimethyl-1-naphthylamine and N,N-dimethyl-2-aminobiphenyl was expected to occur more at the *ortho*-

* It may be noted that lithiation of  occurs on the ferrocene ring, although it has more

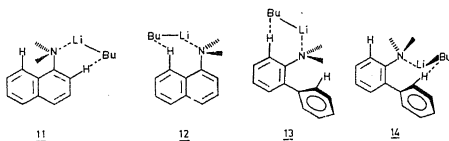
However, actually the lithiation occurred at the distant positions. Thus when N,N-dimethyl-1-naphthylamine was lithiated with *n*-BuLi in ether solution and the metalation mixture treated with benzophenone, the benzhydrol obtained was 7 and not 6. The structure of the compound was established by its NMR spectrum. Here, there was a doublet of doublet ($J = 8$ and 2 Hz) at 6.92δ , which was typical for an aromatic proton with an *ortho* and a *meta* proton neighbours, which was possible only for structure 7. The NOE experiments further established that this was not the proton *ortho* to the NMe₂ group but that *ortho* to the benzhydrol group. Thus no intensity enhancement for the signal at 6.92δ was observed when the signal at 2.2δ , which corresponded to the -NMe₂ group, was irradiated.

Similarly lithiation of N,N-dimethyl-2-aminobiphenyl followed by treatment with benzophenone furnished only the benzhydrol 9 and not 8. In this case, the NMR spectrum was uninformative, but the structure was established by chemical transformation to 10b by first demethylation and then deamination.

Lithiation of N,N-dimethyl-1-naphthylamine and N,N-dimethyl-2-aminobiphenyl at 8- and 2'-positions respectively was surprising. However, it was still consistent with the Roberts-Curtin mechanism and can be explained by taking into account the steric strain present in the transition states corresponding to lithiation at alternate positions. For the lithiation of N,N-dimethyl-1-naphthylamine the transition states, corresponding to lithiation at 2- and 8-positions, are shown in 11 and 12; for the lithiation of N,N-dimethyl-2-aminobiphenyl at 3- and 2'-positions they are 13 and 14. It may be seen that in 11, the two methyl groups on the nitrogen atom are very close to the C-8



Scheme 12



Scheme 13

and H-8 atoms of the naphthalene ring (peri positions) and in 13, they are close to phenyl group at 1-position. The transition states 11 and 13 would be relatively more strained than 12 and 14 respectively. Lithiation then occurs according to the latter, at the distant 8- and 2'-positions respectively, despite the greater acidity of the *ortho*-protons at 2- and 3-positions respectively.

In summary it may be stated that Roberts–Curtin mechanism does explain the orientation observed in all lithiation reactions, reported to date.

Experimental

The m.p.'s are uncorrected; the NMR chemical shifts are in δ scale.

n-BuLi in ether was prepared according to Gilman's procedure (Gilman 1954).

Halogen metal exchange reaction of 1-bromo-2-methoxynaphthalene

(i) in THF solution

To a solution of 1-bromo-2-methoxynaphthalene (2.37 g, 0.01 mole) in THF (50 ml) was added *n*-BuLi (0.01 mole) in ether. The metalation mixture was stirred at room temperature for 1 hr and then treated with DMF (0.73 g, 0.01 mole) in ether (10 ml) during 15 min. It was decomposed with water. The ether layer was separated, and the aqueous layer extracted with ether (3 $\times$ 25 ml). The combined ether layer was washed with water, dried (Na₂SO₄) and the solvent removed. The residue (1.8 g, 96 %) contained only 2-methoxy-1-naphthaldehyde (Narasimhan and Mali 1975) and 2-methoxy-3-naphthaldehyde no other constituents (identified by NMR).

(ii) in ether solution

To a stirred solution of 1-bromo-2-methoxynaphthalene (2.37 g, 0.01 mole) in ether (50 ml) was added *n*-BuLi 0.01 mole in ether. The metalation mixture was stirred for 20 hr at room temperature. It was divided into two approximately equal portions.

One portion was treated with DMF (0.365 g, 0.005 mole) in ether during 30 min. Work-up, as usual, gave a residue which on crystallisation from hexane gave 2-methoxy-1-naphthaldehyde (0.992 g, quantitative yield based on 1-bromo-2-methoxynaphthalene used), m.p. 85° (Narasimhan and Mali 1975, m.p. 85°); NMR identical with authentic sample.

The second portion was treated with a solution of 2-methoxynaphthalene (0.799 g, 0.005 mole) in ether. The reaction mixture was stirred for another 20 hr. It was then treated with DMF (0.365 g, 0.005 mole) during 30 min and then decomposed with water. Usual work-up gave a residue, whose NMR indicated it to be a mixture of 2-methoxy-1-naphthaldehyde and 2-methoxynaphthalene. Chromatographic separation of the residue on silica gel using pet ether for elution gave 2-methoxynaphthalene (0.782 g, 99 %) in the first fraction and 2-methoxy-1-naphthaldehyde (0.876 g, quantitative yield based on 1-bromo-2-methoxynaphthalene used), m.p. 85°.

Halogen metal exchange of 4-bromo-1,3-dimethoxy benzene in ether solution

To a stirred solution of 4-bromo-1,3-dimethoxy benzene (2.17 g, 0.01 mole) in ether

(i) reaction with benzophenone

The metallation mixture was treated with a solution of benzophenone (2.73 g, 0.015 mole) in ether (20 ml), stirred for 10 min, and decomposed with water (50 ml). The aqueous layer was extracted with ether (3×25 ml). The combined ether layer was washed with water and dried (Na_2SO_4). Removal of solvent furnished residue (4.05 g), which was chromatographed on silica gel (150 g) using pet ether for solution. The first fraction gave benzophenone (0.910 g). Further fractions gave 2,4-dimethoxy- α,α -diphenylbenzyl alcohol (3.03 g, 95%, m.p. 138° (Wittig and Pokels 1939, 137.8–138.6).

(ii) reaction with 1,3-dimethoxy benzene

The metallation mixture, prepared as above using 4-bromo-1,3-dimethoxy benzene (1.085 g, 0.005 mole), was stirred with the addition of 1,3-dimethoxy benzene (0.690 g, 0.005 mole) for 5 hr at room temperature and then treated with benzophenone (0.910 g, 0.005 mole) in ether during 3 hr. Decomposition with water followed by usual isolation procedure gave a residue which on chromatography over silica gel using pet ether for elution, gave 1,3-dimethoxy benzene (0.675, 98% recovery) in the first fractions and then 2,4-dimethoxy- α,α -diphenylbenzyl alcohol (1.535, 96%), m.p. 138° .

The same result was obtained when the reaction mixture, after addition of 1,3-dimethoxy benzene, was stirred for 24 hr and then treated with benzophenone.

Lithiation of N,N-dimethyl-1-naphthylamine

To a well stirred solution of N,N-dimethyl-1-naphthylamine (3.0 g, 0.018 mole) in ether (30 ml) was added a solution of *n*-BuLi (0.11 mole) in ether (80 ml). The mixture was stirred for 48 hr at room temperature. Benzophenone (20 g, 0.11 mole) in ether (50 ml) was added and the mixture stirred for 3 hr more, decomposed with water and the ether layer extracted with dil HCl (30 ml). The acid layer was basified with dil NaOH and extracted with ether. Drying (Na_2SO_4) and evaporation of solvent gave residue (4.5 g) which was chromatographed over silica gel (180 g) using benzene for elution. First fractions (500 ml) gave the starting compound (1.5 g, 50%). Next fractions (2000 ml) gave the carbinol **7** (2.8 g, 46%), m.p. 172° (hexane-ethyl acetate); Found: C, 84.72; H, 6.38; N, 3.60; $\text{C}_{25}\text{H}_{23}\text{NO}$ requires C, 84.94; H, 6.50; N, 3.90%; NMR (CDCl_3): 2.2 (6H, s, NMe_2), 6.92 (1H, dd, $J = 8$ and 2 Hz, aromatic H ortho to carbinol), 7.09–7.33 (11H, m, aromatic protons), 7.42 (2H, d, $J = 5$ Hz, one aromatic proton ortho to NMe_2 and the other para to NMe_2), 7.65–7.86 (2H, m, aromatic protons), 11.28 (1H, s, OH, exchangeable with D_2O).

Lithiation of N,N-dimethyl-2-aminobiphenyl

Lithiation of N,N-dimethyl-2-aminobiphenyl (2.0 g, 0.01 mole) as above in ether solution, followed by treatment with benzophenone in ether solution gave a basic residue (3.2 g) which was chromatographed on silica gel (100 g) using benzene for elution. First fraction (1000 ml) gave the starting compound (0.44 g, 22%). Further fractions (2000 ml) gave **9** (2.54 g, 70%), m.p. 198° (hexane-ethyl acetate); Found: C, 85.38; H, 6.57; N, 3.43; $\text{C}_{27}\text{H}_{25}\text{NO}$ requires C, 85.45; H, 6.64; N, 3.69%. NMR (CDCl_3): 2.55 (6H, s, NMe_2), 6.35–7.7 (18H, m, aromatic protons), 8.49 (1H, s, OH,

Demethylation of 9

9 (0.5 g) on heating with HI in sealed tube in N₂ atmosphere at 160° for 36 hr, followed by usual work-up and chromatography on neutral alumina using pet ether for elution gave 10a (0.3 g, 65%), m.p. 140°; Found: C, 85.35; H, 5.92; N, 3.79; C₂₅H₂₁NO requires C, 85.44; H, 6.02; N, 3.99%.

Deamination of 10a

10a (0.05 g) was dissolved in ethanol (0.6 ml) and conc. H₂SO₄ (0.13 ml). The solution was cooled to -4° and a solution of NaNO₂ (0.1 g) in water (0.5 ml) was added. Copper bronze was added and the mixture refluxed on water bath for 30 min. Ethanol was evaporated and the mixture extracted with ether to furnish 10b (0.03 g), m.p. 232°, identical with synthetic sample (mixed m.p., i.r.).

Synthesis of 10b from methyl biphenyl-2-carboxylate

Reaction of PhMgBr with methyl biphenyl-2-carboxylate gave 10b, m.p. 232° (hexane); Found: C, 89.04, H, 6.22; C₂₅H₂₁O requires C, 89.25; H, 5.99%.

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Micellar control of photochemical reactions

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Abstract. Micelles as media for chemical reactions exhibit features that are unique in comparison to ordinary non-aqueous or aqueous solvent media. A thermal or photochemical reaction conducted in micellar media is influenced by the micellar environmental effects resulting in control and/or modification of reactivity. The salient features of micelles and their influence on photochemical reactivity are briefly discussed in this paper.

Keywords. Micelles; cage effect; pre-orientational effect; polarity effect; counterion effect; photochemical reactions.

1. Introduction

The study of photophysical processes and photochemical reactions in ordered molecular assemblies like micelles, microemulsions, vesicles, monolayer films, supported multilayer assemblies and constrained phases like liquid and molecular crystals has added a new dimension to photochemistry (Fendler 1984). Amongst the various ordered molecular assemblies micellar systems have been well investigated. Sensitivity of photophysical processes and photochemical reactions to environmental perturbations have been utilized to probe the nature of micellar aggregates. Understanding the architecture of micelles has helped in its utility as a reaction medium. The potential of micellar effects to bring about catalysis and specificity in photochemical and thermal reactions has been demonstrated. The unique feature of micelles, and how these have been utilized to catalyse and control photochemical reactivity are highlighted in this paper through a brief survey of reports on photochemical reactions in micellar media.

2. Localization, compartmentalization and cage effect

The most striking feature of micelles is the ability to solubilize a variety of compounds. The dynamics of solute partitioning has been studied using luminescence probes. Such studies have revealed that in the time scale 1-100 n sec micelles form physically discrete cells among which the solute molecules distribute themselves. Poisson statistics has been found to be appropriate for this distribution. Poisson statistics leading to solute distribution is given by

$$P(n) = \frac{S^n}{n!} \exp(-S),$$

where $P(n)$ is the probability of finding a micelle with n solute molecules and S is the "mean occupancy number" or ratio of the bulk concentration of solute molecules to a bulk concentration of micelles. It is evident that two situations are possible: (i) The

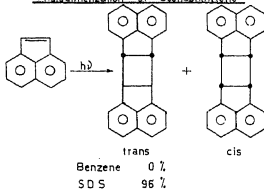
large ($S = 2, 3$). This leads to localization of the reactant and hence extremely high local concentrations favourable for bimolecular reactions. (ii) The substrates concentration is such that most of the micelles are "empty" at any given instant *i.e.* less than 10% of the micelles contain one or more solute molecules ($S = 0.1$). This situation leads to the compartmentalization of the reactants favourable for unimolecular processes. Both these situations have been exploited to control photochemical processes.

Increasing the occupancy number of a micelle and thereby the local concentration of reactant causes an increase in the efficiency of bimolecular photochemical reactions relative to that in non-aqueous or aqueous systems. This is the 'micellar catalysis' effect and has been observed in many bimolecular photochemical reactions. The photodimerization of acenaphthylene (Nakamura *et al* 1977), photocycloaddition of acenaphthylene to acrylonitrile (Nakamura *et al* 1978) and methylacrylate and photocycloaddition of isobutylene to cyclohexenone (Fargues *et al* 1979) (scheme 1) are a few examples which illustrate the local concentration or micellar catalysis effect.

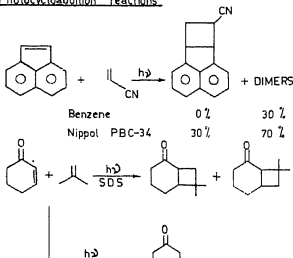
Compartmentalization of reactants is a feature unique to micellar systems leading to the 'protection' of the excited singlet and triplet states of the molecules by suppressing bimolecular quenching processes. The potential of this feature of micelles to selectively effect unimolecular photochemical processes has been demonstrated by Turro *et al* (1978). Solubilization of 1-bromonaphthalene, naphthalene, pyrene and triphenylene in micelles (SDS, CTAC and CTAB) under conditions where multiple occupancy of a micelle was low resulted in the ready observation of phosphorescence from these compounds. Phosphorescence though weak was observable even in aerated micellar media

Scheme 1

Photodimerization of acenaphthylene



Photocycloaddition reactions



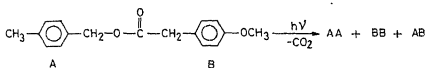
although, under similar conditions, no phosphorescence emission was detectable in organic solvents media. This observation has been attributed to the 'protection' of the triplet states from oxygen quenching and other bimolecular quenching processes like triplet-triplet annihilation and self-quenching. This technique of micellar compartmentalization has been used by Ramesh and Ramamurthy (1982) to inhibit the diffusion-controlled self-quenching process in thioketones. Avoiding multiple occupancy of the micelles, they observed enhanced phosphorescence intensity in nitrogen-purged micellar solutions compared with that in acetonitrile, indicating that thioketone triplet was indeed protected from deactivation by ground state thioketone.

Micellar cage-effect is observed when a hydrophobic radical pair is generated in a micelle. In such a situation the probability of cage reaction between spin correlated radical pairs increases relative to reaction of free radicals without spin correlation.

The photodecarbonylation of unsymmetrical dibenzyl ketones A-CO-B in homogeneous solutions occurs *via* free radicals to produce A-B, A-A and B-B in the statistical distribution of 50:25:25. In contrast when the reaction is conducted in CTAC micelles, a non-statistical distribution of approximately 98:1:1 is obtained (Turro 1983) (scheme 2). Also the yield is a function of CTAC concentration thus exhibiting a significant enhancement of radical cage reactions of hydrophobic radical pairs relative to homogeneous solutions. An interesting aspect of this 'cage effect' of micelles is the observed ^{13}C enrichment of reactants involved in free radical reactions.

The photolysis of dibenzyl ketone (DBK) (scheme 3) proceeds *via* an initial triplet radical pair (3D). Inter-system crossing of a radical pair such as 3D occurs *via* a nuclear hyperfine induced mechanism. Since ^{12}C does not possess a nuclear moment, hyperfine radical pairs with ^{13}C will undergo more rapid inter-system crossing than radical pairs with ^{12}C . Scheme 3 shows the various processes possible. Since 1D and $^1D'$ radical pairs

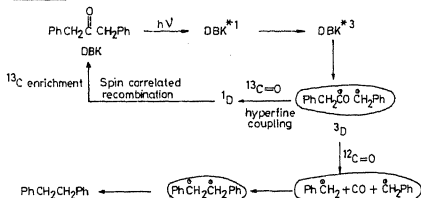
Scheme 2



i - Propanol 1 : 1 : 5

Micelle (KDC) 1 : 1 : 50

Scheme 3

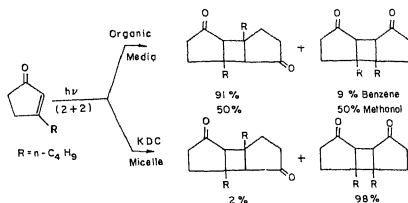


dodeconoate (KDC) micelles leads to greatly increased efficiency of dimerization over that in homogeneous solution. Irradiation of 3-*n*-butyl and 3-*n*-decylcyclopentenone in KDC micelle leads to complete reversal in regioselectivity with the formation of the compounds corresponding to head-head dimer 98 % (scheme 5). These dimerize in organic solvents to the corresponding head-tail dimer in preference to the head-head dimer although the ratio of head-tail to head-head approaches 1:1 methanol and acetonitrile (scheme 5). However the complete reversal in micelles has been ascribed to a specific micellar effect and is suggested that it is not due to the polarity of the medium. Preorientation is expected to be the result of the enones being oriented with the carbonyl group in the Stern layer and the alkyl group in the core. These results have been successfully extended to mixed cycloadditions between 3-alkylcyclopentenones and olefins with a reversal in regioselectivity as compared to that in organic solvents (Berenjian *et al* 1982).

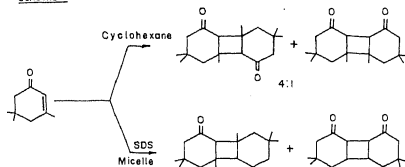
Dimerization of isophorone (scheme 6) has been shown to be enhanced in micellar and microemulsion systems (Fargues *et al* 1979, 1982). Formation of dimers in organic solvents depends, as in the previous case, on the polarity of the medium. Head-tail dimers are formed as major products in nonpolar solvents while polar solvents enhance head-head dimerization. In micellar media head-head dimers are formed in high yields, presumably due to the micellar alignment effect.

Nakamura *et al* (1981) have obtained a similar reversal in regioselectivity of the 4 + 4 dimerization of 2-pyridones. These dimerize in ethanol to give the corresponding *trans* dimers as the major product. In CTAB appropriate substitution of 2-pyridones by long chains leads to a reversal in regioselectivity (scheme 7). Similarly in the case of

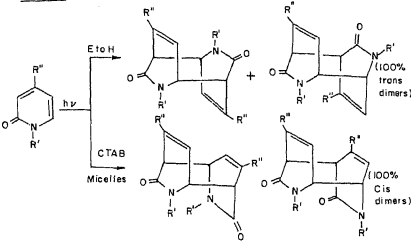
Scheme 5



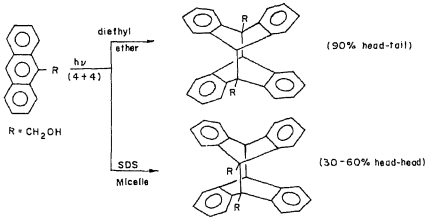
Scheme 6



Scheme 7

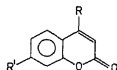


Scheme 8



photodimerization of (hydroxymethyl) anthracene (Wolf 1981), formation of the $head-head$ dimer is promoted in micellar media (scheme 8).

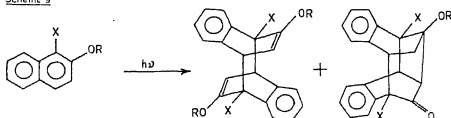
The above examples demonstrate the general usefulness of the micellar alignment to achieve regioselectivity. However, Muthuramu *et al* (1983) have shown that the micellar alignment effect has limitations. 7-Alkoxy-coumarins which dimerize in solvents to give the corresponding syn head-tail dimer, irrespective of solvent were used as models to eliminate any polarity effects due to the polar Stern radiation of the shorter chain coumarins ($n = 0-5$) (figure 1) in micellar media. It led to the expected reversal in regioselectivity during photodimerization in contrast to the effective reversal observed by the previous workers with chain lengths of $n = 0-5$ with other systems. The chain lengths were increased beyond five upto $n = 10$ with the expectation that the accompanying increase in hydrophobicity of the molecules would lead to more effective micellar alignment. However, contrary to the expectation no reversal in regioselectivity was obtained. This led to the conclusion that the micellar orientational effect is most effective only in those systems where the forces of micellar regiochemistry are weaker than the hydrophobic association energies

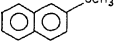
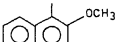


- | | |
|--|---|
| 1 R = H ; R' = OCH ₃ | 10 R = CH ₃ ; R' = OCH ₃ |
| 2 R = H ; R' = O(CH ₂) ₃ CH ₃ | 11 R = CH ₃ ; R' = O(CH ₂) ₃ CH ₃ |
| 3 R = H ; R' = O(CH ₂) ₅ CH ₃ | 12 R = CH ₃ ; R' = O(CH ₂) ₅ CH ₃ |
| 4 R = H ; R' = O(CH ₂) ₆ CH ₃ | 13 R = CH ₃ ; R' = O(CH ₂) ₆ CH ₃ |
| 5 R = H ; R' = O(CH ₂) ₇ CH ₃ | 14 R = CH ₃ ; R' = O(CH ₂) ₇ CH ₃ |
| 6 R = H ; R' = O(CH ₂) ₁₁ CH ₃ | 15 R = CH ₃ ; R' = O(CH ₂) ₁₁ CH ₃ |
| 7 R = H ; R' = O(CH ₂) ₁₃ CH ₃ | 16 R = CH ₃ ; R' = O(CH ₂) ₁₇ CH ₃ |
| 8 R = H ; R' = O(CH ₂) ₁₅ CH ₃ | |
| 9 R = H ; R' = O(CH ₂) ₁₇ CH ₃ | |

Figure 1. Methoxycoumarins investigated in micelles.

Scheme 9



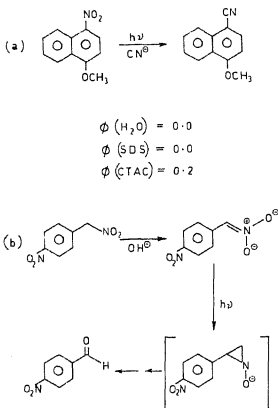
	Benzene	80	—
	S D S	—	60
	CTAB	—	30
	CTAC	—	71
	DTAC	—	67
	Cyclohexane	50	45
	S D S	—	45
	CTAB	—	12
	CTAC	—	61
	DTAC	—	65

dipole forces (Teitei *et al* 1978). Photodimerization in micellar media lead to *cis* dimer derived products, although the major product in homogeneous media is the corresponding *trans* dimer (scheme 9) (Ramesh and Ramamurthy 1984).

4. Charged micelle-water interface

The aggregation of ionic amphiphiles leads to the distribution of ionic head groups and counter-ions such that a charged micelle-water interface results. The electrically-charged interface has been utilized to accelerate or retard reaction rates between micelle-solubilized substrate and an ionic reactant in the aqueous exterior. Depending on whether the charge of the detergent causes repulsion of attacking nucleophile or

Scheme 10



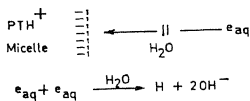
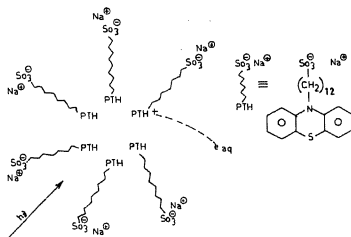
Such effects have been utilized in the photoinduced substitution reactions of aromatic compounds. Photoinduced conversion of 4-methoxy-1-nitronaphthalene to 4-methoxy-1-naphthalene-carbonitrile (Hautala and Letsinger 1971); and photo-rearrangement of 4-nitrobenzaldehyde (Yamada *et al* 1978) (scheme 10) illustrate the influence of this effect.

The charged micelle water interface plays an important role in light energy storing photoreactions (Alkaitis and Gratzel 1976). It has been demonstrated that when functional micelles with attached redox chromophore (*e.g.* sodium 12-(10'-phenethiazinyl)dodecylsulphenate) are irradiated hydrated electrons and cations are produced monophotonically in high yield. This effect has been explained in terms of photoejection of electrons from the micellar into the aqueous phase and subsequent stabilization of the radical ions by the charged micelle water interface. The latter acts as a Schottky barrier, preventing the approach of hydrated electrons and parent ions. Schematic illustration of the process is given in scheme 11.

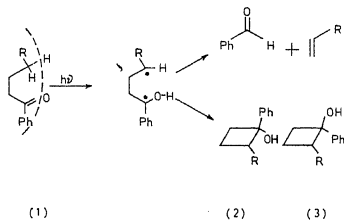
5. Polarity effect

It has been established that aromatic molecules and substrates bearing hydrophilic groups are solubilized at the micelle-water interface which is a region of high polarity.

Scheme 11



Scheme 12



$R = n - C_4H_9$

Phenyl heptyl ketone

Cyclobutanols

Medium	ϕ	Ratio (2)/(3)
t-BuOH	1.0	1.5
C ₆ H ₆	0.33	4.7
CTAC	0.7	1.2

5/6 is 1.2. These values are much closer to those for type II reaction in *t*-BuOH ($\phi = 1.0$, 5/6 = 1.5) than those in benzene ($\phi = 0.33$, 5/6 = 4.7) thus suggesting that the environment around the site of solubilization of the ketone is polar. Recently, Winkle *et al* (1983) arrived at similar conclusions.

Coumarin dimerizes in solution to give four different dimers. The syn head-head and head-tail dimers are generally predominant in polar solvents. Muthuramu and Ramamurthy (1982) observed that in micellar media as SDS and CTAB, the reactivity and emission intensity of coumarin are enhanced significantly. Also, the syn head-head dimer is the sole product in these micelles. Selectivity in the formation of the dimer and enhanced reactivity are attributed to the polar environment in which coumarin undergoes dimerization.

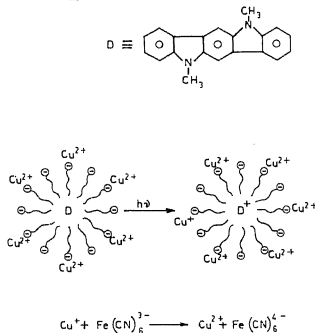
6. Counterion effects

Ionic micelles have the property of being able to bind oppositely charged ions. This aspect together with their ability to solubilize hydrophobic molecules has been utilized in reactions involving organic substrates and metal ions.

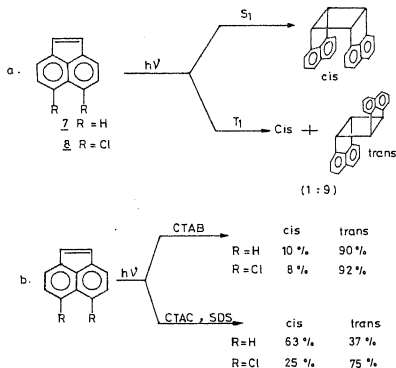
For example, it has been shown that adsorbed metal ions on anionic micelles can act as efficient electron acceptors from excited micelle solubilized donors (Mori *et al* 1979). The replacement of the Na ions in sodium dodecyl sulphate by Cu^{2+} yields assemblies in which Cu^{2+} ions constitute the counterion of the micelle. Donor molecules like N,N'-dimethyl-5,11-dihydroindole [3,2-b] carbazole (D) when incorporated into such micelles and irradiated leads to extremely rapid electron transfer from excited singlet state of D to Cu^{2+} counterion. The Cu^+ formed in the aqueous phase can be used for a second redox process such as reduction of $\text{Fe}(\text{CN})_6^{3-}$. The back reaction of the $\text{Fe}(\text{CN})_6^{4-}$ with the oxidized donor, D, is prevented by the negatively-charged micellar surface. Such a system, therefore, has been successful in storing light energy originally converted into chemical energy during a photoredox process. Schematic representation of the counterion effect in this process is depicted in scheme 13.

Yet another feature of counterions is that they function as heavy atoms. Kalyanasundaram *et al* (1977) have shown that by replacing Na ions of sds by Tl ions the rate of phosphorescence of aromatic hydrocarbons like a naphthalene and pyrene solubilized in such micelles can be enhanced at room temperature. This observation has been attributed to the heavy atom counterion-induced intersystem crossing of aromatic excited singlet states to triplet states. The above observations suggest that by using micelles with differing counter ions it may be possible to attain state selectivity in the reactive state of a photochemical reaction or photophysical processes. Wolff (1982) observed that the quantum yield of fluorescence of excited aromatic molecules such as substituted anthracenes, indenenes and N,N-diphenylamine show an increase in CTAC as compared to CTAB and conversely, exhibit lower quantum yield of triplet formation in CTAC as compared to CTAB. An interesting observation is the enhancement in triplet state derived products from the photodimerization of acenaphthylene. Irradiation of acenaphthylene in solution has been studied extensively. It has been established that the excited singlet yields exclusively the *cis* dimer (scheme 14) while the triplet state yields a mixture of *trans* and *cis* dimers in the ratio 9:1 (scheme 14). Ramesh and Ramamurthy (1984) and Meyer and Seaver (1983) independently found that the *cis/trans* ratio in cyan

Scheme 13



Scheme 14



concentration of the reactant (1.3 mM as compared to 8 mM in the above case) the photodimerization is almost exclusively *via* the triplet channel in CTAB, whereas in CTAC, DTAC and SDS micelles singlet state derived *cis* dimer still predominates. The low *cis/trans* ratio has been attributed to the "external heavy atom effect" of the bromide counter ions which are suggested to enhance the $S_1 \rightarrow T_1$ intersystem crossing *via* intermolecular spin-orbit coupling and the triplet-derived *trans* dimer yield is increased. Similar observations have been made in the case of 5,6-dichloro-

media suggest that for photochemical reactions that proceed *via* competing singlet and triplet states, state selectivity can be achieved by utilizing heavy atom counter ions for triplet state product and light atom counter ions for predominantly singlet state products. However, this technique has its limitations. Firstly, the photochemical reaction should be sensitive to heavy atom effect. Secondly, the $S_1 \rightarrow T_1$ intersystem crossing should be more sensitive to heavy atom perturbation than $T_1 \rightarrow S_0$. If the latter is more sensitive, then using micelles having heavy atom counter ions will result in a reduction in the yield of triplet derived products.

In view of the great potential of micellar systems as media for conducting reactions a clear understanding of the structure of micelles is very essential. An intimate knowledge of the precise molecular structure of micelles certainly would help the more intelligent exploitation of micelle-mediated processes. One can foresee much activity in the coming years on control of reactivity using micelle and micelle-like systems.

Acknowledgements

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Chemical modelling of photosynthesis: Intramolecular quinone-porphyrin complexes

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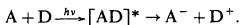
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Abstract. The strategies for the synthesis of covalently linked, flexible and rigid quinone-porphyrin complexes are described. Several anomalous chemical reactivities were observed in the quinone-capped porphyrins which may be attributed to the proximity of quinone and porphyrin moieties. Previous investigations by ^1H NMR spectroscopy have demonstrated that the metal ion in capped metalloporphyrins is 5 co-ordinate, bound intramolecularly to quinone carbonyls and can accept a sixth ligand from the unhindered side. Here, additional evidence from ^{13}C NMR spectroscopy is presented to support the intramolecular co-ordination of the quinone and establish the cooperativity in binding of an external ligand; this process involves the movement of the metal ion into the porphyrin plane, pulling the quinone chromophore closer to the porphyrin. Electrochemical results reveal that the quinone in capped metalloporphyrins are better electron acceptors than simple quinones. The intramolecular quinone-porphyrin complexes promise to be potential model compounds to demonstrate the primary photosynthetic event *in vitro*.

Keywords. Photosynthetic modelling; quinone-porphyrin complexes.

1. Introduction

The primary photochemical process in algal and green plant photosynthesis is known to involve a one-electron transfer reaction from a chlorophyll donor species to an electron-acceptor molecule, the electron transfer taking place across the thylakoid membrane within a special reaction centre. There have been numerous laboratory approaches to mimic this reaction *in vitro*, the objective being to achieve a stable charge separation after the electron transfer from the excited donor (D) to the acceptor (A).



A special arrangement of the donor-acceptor molecules *in vivo* permits efficient electron transfer and to achieve this *in vitro*, experimental attempts have centred around studies on catalytic and modified chlorophylls, porphyrins and other chromophores. Among the various factors responsible for an efficient electron transfer are the relative oxidation-reduction potential of donor-acceptor system, chromophore separation, relative orientations and absorption characteristics. Since all these factors are amenable to a rational control by chemical synthesis, a new class of molecules, "quinone-porphyrins", have emerged in which the two chromophores are covalently linked. This article is intended to highlight the various synthetic approaches, interesting photochemical and spectroscopic properties of these intramolecular complexes, which promise to be potential non-biological models for the primary photosynthetic event.

One of the prime motivating factors for studying the covalently linked quinone-porphyrins arises from the fact that simple irradiation of porphyrins or metallo-porphyrin complexes in the presence of quinone does not lead to an effective separation

or the oxidizing species (porphyrin radical cation) and the reducing species (quinone radical anion). At low concentrations of the electron acceptor, the large separation between the donor and acceptor molecules may result in an inefficient electron transfer, whereas at high concentrations the two species may be too close resulting in a fast recombination of charges. In frozen or aggregated states, the structural features are not well defined to systematically probe the structure-function relationships. In view of these facts, quinones which are covalently bonded to porphyrin framework are of interest in evaluating the structure and photochemical properties and as aid in the molecular engineering of a synthetic photosystem.

Structurally, two classes of quinone-porphyrins can be recognised: (i) quinone-tailed porphyrins in which a quinone moiety is linked through spacer groups to a porphyrin at the meso position either directly such as (1) and (2) or through a phenyl substituent at meso position, *e.g.* (3) and (4) and (ii) quinone-capped porphyrins (5–8) in which the diagonal pyrroles are connected by a bridge which spans across one face of the porphyrin and contains a quinone function. The following sections discuss separately these two classes of molecules.

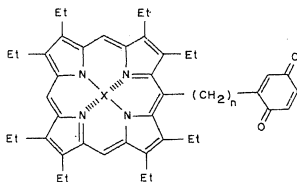
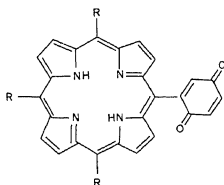
2. Quinone tailed porphyrins

2.1 General synthetic approach

The general synthetic approach to this class of porphyrins involves an initial preparation of unsymmetrically substituted porphyrins. This is achieved by a slight modification of the general procedure (Adler *et al* 1967) which involves condensation of equimolar amounts of pyrrole and an aldehyde. For unsymmetrically substituted porphyrins, a second aldehydic component is added in stoichiometric amounts to the reaction mixture (Kong and Loach 1980). This leads to a mixture of products in which either some or all phenyl rings at the meso positions carry substituents. The ratio of products can be controlled by the stoichiometry of the starting aldehydes and the separation of products effected by chromatography. The functional group on the phenyl rings are then used as anchor points to append the benzoquinone through a spacer chain. The quinone functions are masked either as dimethyl ethers or as diacetates at the stage of condensation with the porphyrin. On deprotection under mild conditions (*e.g.* BBr_3 in CH_2Cl_2), one obtains the hydroquinone-porphyrins which are converted into quinone-porphyrins with oxidizing agents such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or lead dioxide in benzene. By varying the length of the spacer chain, the distance between the two chromophores can be controlled and the point of anchor on the porphyrin can be *o*-, *m*- or *p*-position on the phenyl ring. These possibilities allow a subtle control over the orientation of the two chromophores in the final product. When the starting porphyrin has no aromatic substituents at meso position such as that required for (1), Vilsimier reaction introduces an aldehyde group at the meso position; this after reduction to a hydroxymethyl group serves as an extension point to add the quinone chain (Nishitani *et al* 1981).

2.2 Spectral characterisation

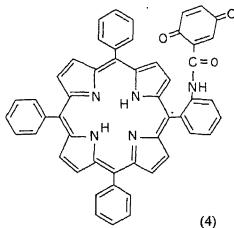
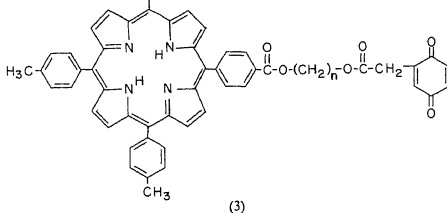
The uv-visible absorption spectrum of the quinone-linked porphyrins exhibit no major changes compared to unlinked entities except in case of (2). They are almost identical to

(1) $n = 2, 4$ and 6 , $X = H_2$ and Zn 

(2)

a 1:1 addition spectrum of the two components and hence indicate no appreciable interaction between the two chromophores in ground state. In case of (2) the uniform symmetrical broadening of the Soret (B band) and visible (Q bands) regions becomes more pronounced on addition of acid (Dalton and Milogram, 1982). It has been suggested that the broadenings may be either due to a vibrational modulation of the porphyrin excited state by quinone or due to charge transfer interactions between the two chromophores (Bergkamp *et al* 1982).

One of the characteristic features of 1H NMR of porphyrins is the upfield shifts of certain resonances located above the plane of the porphyrin. This is due to the large ring current generated by the 18π electron system and the magnitude of such shifts can be correlated with the spatial proximity of the protons to the porphyrin plane. Specifically, the protons of the hydroquinone and quinone moieties in the linked quinone-porphyrin complexes exhibit large upfield shifts compared to their corresponding positions in unlinked species, for *e.g.* in the hydroquinone form of (4), the H_1 , H_2 and H_3 protons are upfield shifted by 2.9, 1.4 and 1.6 ppm, but on oxidation to the quinone (4), the ring current induced shifts change to 0.1, 2 and 3 ppm respectively (Tabushi *et al* 1979). This suggests that both quinone and hydroquinone moieties are located in close proximity to the porphyrin plane in both these molecules but are in quite different orientations. Similar effects are noticed in other quinone-porphyrins (Kong and Loach 1980). Significantly, on metallation of the complexes the upfield shifts are increased, indicating a much more favourable interaction between the two chromophores. This



2.3 Fluorescence and electron transfer studies

Quinones are known to quench porphyrin excited states in a bimolecular reaction and the extent of quenching depends on the concentration and the reduction potentials of the quinones. All quinone-porphyrins exhibit very low fluorescence spectrum and by interpolating the benzoquinone concentration-dependent fluorescence data of tetraphenylporphyrin, the effective concentration of quinone to quench TPP fluorescence intramolecularly is estimated in (4) to be 4.2×10^{-2} M (Tabushi *et al* 1979). This indicates a more favourable interaction of the two chromophores in the linked molecules compared to the free intermolecular reaction. In a similar study by Nishitani *et al* (1981), the relative quenching efficiency in different intramolecular complexes (1) over the free component mixtures was in the range 700 to 5000; the shortening of polymethylene chain ($n = 2$) and coordination with the metal resulted in larger quenching efficiencies. Though these results indicate an effective donor-acceptor combination in these systems they alone do not prove that photochemical electron-transfer has taken place. The direct evidence for this comes from the steady state and transient EPR measurements in the linked molecules (3) (Ho *et al* 1980). When the unlinked components of (3) are photolysed in methanol at low temperatures (160 K) an irreversible intermolecular electron transfer is observed when the concentration of quinone is about 1000 times that of porphyrin, as indicated by the formation of

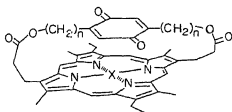
quinone radical anion. On the other hand the electron transfer in the linked molecules (3) was found to be reversible at 160 K but irreversible at lower temperatures (140 K). The quantum efficiency of the production of EPR signal by photolysis in unlinked molecules was much less than that of linked species at equivalent concentrations. The electron transfer kinetics in the linked molecules was similar to that in the natural system and suggested a range of activation energies for the electron to return to the primary donor. This may be due to the relative motions of the donor-acceptor ends of the tailed molecules caused by the various conformations of the intervening hydrocarbon chain. In order to circumvent this type of diffusional and configurational uncertainties prevailing in the quinone-tailed porphyrins, the more rigid quinone-capped porphyrins have been synthesised by us (Ganesh and Sanders 1980) and their properties are discussed in the following section.

3. Quinone-capped porphyrins

These systems are attractive for various reasons. The distance between the quinone and porphyrin can be carefully controlled by merely varying the size of the bridge. This would enable study of the effect of distance and molecular structure on the kinetics and mechanisms of the intramolecular electron transfer processes. The bridge can be designed either to facilitate or to prevent intramolecular binding between the quinone and central metal ion. This allows a rational control of the co-ordination chemistry which may be usefully employed to influence the chromophore orientation and hence the electron transfer characteristics. In addition, these systems would be ideal to investigate radical induced NMR effects since both porphyrin radical cations and quinone radical anions can be generated selectively by chemical means. These studies may eventually be valuable in the study of chlorophyll-protein complexes. The capped porphyrins have received wide attention recently (Bogatskii and Zhilana 1982) in studies related to oxygen binding properties and synthetic systems related to haem proteins.

3.1 Synthesis

There are two approaches to the synthesis of capped porphyrins. One approach involves a direct condensation of a bifunctional porphyrin such as (9) with the capping constituents which are also bifunctional. In the second approach, the bridge is preformed with the porphyrin precursors built on the two ends and cyclised



(5) $n = 2$; $X = H_2$

subsequently by an intramolecular condensation. An excellent review by Bogatskii and Zhilana (1982) describes the various synthetic approaches to the bridged porphyrins. The details of the synthetic route to the quinone-capped porphyrins are described elsewhere (Ganesh and Sanders 1982) and here we mention only three interesting chemical properties observed during the chemical synthesis, which arise as a consequence of bringing the two chromophores close in space.

(i) The quinone function was protected as the diacetal (methoxy methyl) during the condensation with the porphyrins. All attempts to deprotect this group with aqueous dilute mineral acids failed, though under similar conditions the porphyrin free components reacted smoothly. In all cases, the formation of porphyrin dications could be inferred on the basis of UV-visible spectra. The proximity of the porphyrin dications presumably inhibits the acetal protonation and deprotection to the hydroquinone was eventually achieved with BCl_3 .

(ii) The oxidation of the hydroquinone-capped porphyrins to the quinone-porphyrins with lead dioxide was at least five times rapid compared to normal hydroquinones. The capped hydroquinones were unstable and produced free radicals on standing at room temperature (presumably semiquinone radical ion) as detected by broadened NMR signals. This modified red-ox behaviour of hydroquinones when in close proximity to the porphyrin is corroborated by electrochemical results described in §3.4.

(iii) One expects the capped porphyrins to be difficult to metallate because of the steric constraints to the axial approach of the metal. On the contrary, the bridged porphyrins could be metallated at least 3 times faster than simple porphyrins. Such rapid metallations seems to be a general feature of capped porphyrins irrespective of whether the cap is functionalised with a co-ordinating group or not. The source of this reactivity may reflect either the higher oxidation potential of the free-base porphyrin or the greater accessibility of the central N-H protons in a nonplanar macrocycle severely distorted by the bridge.

3.2 Spectral characterisation

The main characteristic features of ^1H NMR of capped porphyrins centre around the large ring current induced upfield shifts observed for the cap protons. A detailed analysis of the ^1H NMR spectra in these and related systems to elucidate the molecular shape, motions and flexibility has been presented earlier (Ganesh *et al* 1982) and the following picture emerges as a consequence.

(i) The bridged porphyrins are chiral on the NMR time scale *i.e.* racemisation by flipping the cap from above to below the macrocycle takes seconds at least. This causes the non-equivalence of geminal protons on the propionate side chain, which occur as complex multiplets (figure 1). The analysis of vicinal and geminal coupling constants together with nuclear Overhauser enhancements (nOe) for the propionate side chain protons favours a *trans* relationship between the porphyrin and the carbonyl group of the propionate ester. It may be pointed out that the crystal structure of two other related compounds by Cruse *et al* (1980) indicates a *gauche* relationship between these

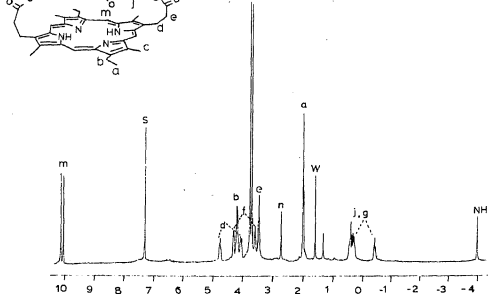


Figure 1. 400 MHz ^1H NMR spectrum of (7) in CDCl_3 . The chemical shifts are in ppm on scale. S = Solvent, W = Water.

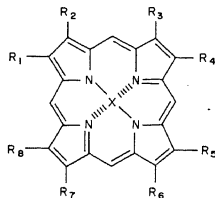
times in the capped porphyrins than for simple porphyrins. The slower motions are due to the “cap” which severely hinders the motion causing relaxation *i.e.* spinning around the four fold axis.

(iii) The lone signal observed for the quinone proton (n) arises by a fast exchange process which averages the different conformations possible for the cap. This averaging can occur with the quinone ring being either parallel or perpendicular to the porphyrin plane. The cap fragment C–C–quinone–C–C– is essentially planar though rotational averaging around C–C bond is permissible. The closer proximity of the quinone cap to the porphyrin indicated by ^1H NMR in compounds with flexible bridges (8, 9) compared to rigid ones (6, 7) seems to be a general feature of bridged porphyrins since similar results have been noticed in other cases (Baldwin *et al* 1981). The remarkable temperature dependent chemical shifts observed for the quinone and protected hydroquinone precursors of these porphyrin derivatives agrees with a picture in which the interchromophore distance increases with temperature and decreases on cooling.

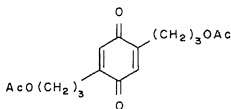
(iv) UV visible absorption spectra of the capped porphyrins show only small differences from simple porphyrins indicating little optical interaction between the two chromophores. This lack of substantial interchromophore interaction may partly be explained by the orientational dynamics of the quinone cap as revealed by ^1H NMR results.

3.3 Intramolecular co-ordination chemistry

The addition of molar equivalents of pyridine to solutions of the capped metalloporphyrins (6) and (8) in CDCl_3 results in large upfield shifts for the pyridine and cap protons. This is due to the porphyrin ring current and for pyridine the effect is largest on the α -protons and progressively decreases with β - and γ -protons. The pyridine shift ratios β/α and γ/α (table 1) are therefore sensitive to the co-ordinate distance between



- (9) $R_1 = R_3 = R_5 = R_7 = \text{Me}$, $R_4 = R_8 = \text{Et}$, $R_2 = R_6 = \text{CH}_2\text{CH}_2\text{COOMe}$, $X = \text{H}_2$.
 (10) $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = \text{Et}$, $X = \text{Mg}$
 (11) $R_1 = R_4 = R_5 = R_8 = \text{Me}$, $R_2 = R_3 = R_6 = R_7 = \text{Et}$, $X = \text{Mg}$
 (13) $R_1 = R_3 = R_5 = R_8 = \text{Me}$, $R_2 = R_4 = \text{Et}$, $R_6 = R_7 = \text{CH}_2\text{CH}_2\text{COOMe}$, $X = \text{H}_2$
 (14) (13) with $X = \text{Mg}$.



(12)

Table 1. Pyridine shift ratios* and binding constants (K).

Compound	β/α	γ/α	K	Co-ordination
(11)·Py†	0.315	0.263	—	5
(11)·2 Py†	0.309	0.264	—	6
Mg·TPP·Py†	0.275	0.241	—	5
Mg·TPP·2 Py†	0.269	0.206	—	6
(10)·2 Py	0.317	0.250	$4.25 \times 10^5 \text{ mol}^{-2}$	6
(8)·Py	0.312	0.260	25.2 mol^{-1}	6

* Limits of error: $\beta/\alpha \pm 0.005$, $\gamma/\alpha \pm 0.01$.

† Values quoted from Storm and Corwin (1964); TPP = tetraphenyl porphyrin.

the metalloporphyrin and pyridine. For example the smaller β/α ratio for tetraphenylporphyrins may result from the phenyl substituents which sterically prevent the closer approach of the ligand to the metal. The evidence for pyridine binding on the unhindered face of the capped porphyrins comes from the fact that shift ratios observed with these molecules are similar to those observed with simple porphyrins. The binding constants for pyridine with capped porphyrins are many orders of magnitude weaker than the usual first ligand binding to a magnesium porphyrin and are rather similar to a second binding. These facts together with the pattern of shifts observed for the cap

in the absence of added external ligand binds a quinone carbonyl as fifth ligand and is displaced out of the porphyrin plane towards the cap (figure 2). Addition of an external ligand such as pyridine which binds on the unhindered side, pulls the metal into the plane; the metal in turn pulls the cap closer to the porphyrins. This cooperative intramolecular binding of quinone to the central metal atom should perturb the electron densities at the skeletal carbons of the porphyrin and quinone chromophores. Since the carbon nuclei in unsaturated systems are more sensitive than protons to long range electron donating and withdrawing substituents, we have studied the ^{13}C NMR of capped porphyrins (table 2). Several interesting conclusions follow from these results.

The chemical shifts of carbons from the cap of the molecule (*q*, *n*, *y*, *g*, *j* and *f*) are all upfield compared to their shifts in simple quinones, due to the ring current of the porphyrin. The absolute magnitude of such induced shifts is the same for both ^1H and ^{13}C but seems less prominent for ^{13}C whose intrinsic chemical shifts are spread over 200 ppm. Any intramolecular binding of quinone is expected to decrease the electron density from the quinone, leading to a downfield shift of the quinone carbon resonances. Consistent with this, the metallation of the capped porphyrins induces a downfield shift on all the carbons of the cap and especially on the quinone carbonyls (*q*). The observation of a single carbonyl resonance indicates that the quinone carbonyls are in fast exchange for the co-ordination site on the metal and so are indistinguishable. Addition of pyridine to the metalloporphyrin (8) shows increased upfield shifts of the cap resonances, particularly the carbonyls and this may be explained as due to the pulling of the cap closer to the porphyrin by the metal when it becomes 6 coordinate species.

The slight downfield shifts observed for the meso carbons (*m*, *m'*) and ring methyls

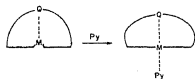


Figure 2. 5 and 6 co-ordinate complexes of quinone capped metalloporphyrins.

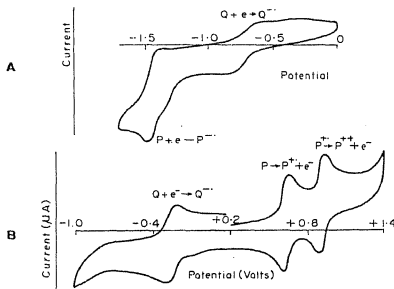


Table 2. ^{13}C Chemical shifts*.

Compound	a	b	c, c'	d	e	f	g, j	n	m, m'	y	s	q	β	α
(9)	17.5	19.5	10.7 11.1	21.8	37.3	52.0	—	—	96.1 96.3	—	173.4	—	133.7 136.9 (br)	140.5 (br)
(12)	—	—	—	—	20.6	63.5	25.0 26.6	133.3	—	148.4	171.0	186.0	—	—
(7)	17.5	19.7	11.3 11.8	24.8	36.8	63.3	22.2 22.6	127.0	96.4 96.9	144.0	174.3	183.4	127.4 128.3 140.8	138.3 141.4
(8)	17.5	19.6	11.3 11.5	24.7	37.6	61.7	22.5 22.8	130.5	97.7 98.2	146.8	174.0	185.6	136.2 137.5 138.0	147.1 147.4 147.8
(8) + pyridine	17.6	19.9	11.2 11.6	25.5	37.2	61.7	22.6 22.7	128.5	97.7 98.0	144.8	174.2	183.8	143.2 137.6 143.2	147.4 147.1 147.8 147.4 148.4

* All samples were run in CDCl_3 , on Varian XL-100-12A at 25.2 MHz for ^{13}C . The values are in δ units, concentration 30 mM and temperature 26°C.

(c, c') in capped porphyrins compared to simple porphyrins may suggest a weaker ring current in the capped molecules. Such decreases in the ring current could arise in porphyrins which are non-planar due to the strain induced by the bridge. This may also suggest an explanation for the greater ease of metallation of these molecules where the non-planar structure results in greater accessibility of the central N-H protons by the metal ion. The metallation also causes an upfield shift of the f carbons which may presumably result from a simple movement of this carbon into the ring current area as a result of the conformational changes induced in the bridge. Not much significant influences are noticed on the chemical shifts of the quaternary carbons (α , β), of the porphyrin ring. The origin of the observed changes in ^{13}C shifts though partly is due to steric factors (such as conformational changes) in addition to the electronic effects, the shifts yet qualitatively confirm the coordination picture derived from ^1H NMR.

3.4 Electrochemistry

It was pointed out earlier that some unusual red-ox properties were noticed during the chemical synthesis of the quinone-capped porphyrins. Because of the obvious importance of the radicals from these compounds, we have done preliminary electrochemical experiments to establish the red-ox states (table 3) by using cyclic voltametry. The capped metalloporphyrin (8) shows two one-electron oxidations in the potential range scanned ($-1.7\text{ V} + 1.4\text{ V}$) (figure 3) whereas its free base porphyrin (7) exhibits single one-electron oxidation, all processes being electrochemically reversible. This behaviour is similar to those observed with simpler porphyrins but the measured half wave potentials ($E_{1/2}^0$) reveal interesting information. The $E_{1/2}^0$ for the first oxidation of porphyrin in (7) is more positive by 0.14 V compared to simpler porphyrins meaning that the former are more difficult to oxidise than the latter; metallation decreases this margin to 0.07 V . For free base porphyrin (7) $E_{1/2}^0$ for quinone reduction is more negative by 0.25 V indicating that this process is more difficult than in simple quinones. However, the situation is reversed on metallation; the quinone reduction in capped metalloporphyrin (8) is now easier by 0.3 V compared to free quinones. This is a very encouraging result from the point of photochemical electron transfer reactions and also explains the facile oxidations observed during the chemical synthesis. The addition of pyridine does not show significant deviations in the $E_{1/2}^0$ values but the electrode processes seemed more irreversible. From the shape of the

Table 3. Half-wave potentials*.

Compound	$P \rightarrow P^+ + e^-$	$P^+ \rightarrow P^{++} + e^-$	$Q + e^- \rightarrow Q^-$	$P + e^- \rightarrow P^-$
(12)	—	—	-0.5	—
(13)†	0.78	—	—	-1.34
(14)†	0.54	0.94	—	—
(7)	0.92	—	-0.75	-1.4
(8)	0.61	0.89	-0.2	—
(8)† pyridine	0.61	0.85	-0.23	—

* Reference electrode = Ag/AgCl , Working electrode: platinum, electrolyte 0.1 M Tetrabutyl ammonium perchlorate, solvent: dichloromethane, Temp: 25°C , All values are in volts.

voltammo grams, the formation of anions of porphyrin and quinones can be observed as separate processes, but the possibility of intramolecular electron exchange between them cannot be ruled out.

The nanosecond photochemistry of the capped porphyrins shows substantial but undramatic deviations from the unlinked molecules; the fluorescence lifetime of the capped molecules are only 3 times shorter than simple porphyrins. More detailed investigations are needed on this aspect before meaningful conclusions are drawn about the photochemical properties of these compounds. One common feature in all the above systems is that the porphyrin and quinone components are present in a stoichiometric ratio of one. Since the energy transfer also depends on the relative concentrations of the donor and acceptor molecules, we have synthesised molecules in which two quinones are attached to a single porphyrin (porphodiquinones*) and the spectroscopic results on these molecules will be reported shortly.

3.5 Conclusions

The synthetic routes to covalently linked quinone-porphyrins are now established and meets many of the prerequisites demanded for a synthetic photosystem such as easy variation of interchromophoric distances and relative red-ox potentials. In capped porphyrins the quinone ring is mobile on NMR time scale to average the chemical shifts, though CPK models indicate considerable hindrance to such motions. The quinone binds intramolecularly to the central metal atom as shown by ^1H and ^{13}C NMR spectra; in spite of such a binding, the two carbonyls cannot be distinguished since they are in fast exchange process for ligation site on the metal. The metal atom is 5-coordinate in capped porphyrins but accepts a sixth ligand to become 6 coordinated, the latter being a weaker process. The introduction of bulky substituents into the cap may prevent intramolecular binding and such control over the coordination chemistry may eventually be useful to orient the two chromophores for a favourable photochemical interaction. Electrochemical results reveal that the quinone in capped metallo-porphyrins is a better electron acceptor (easy reduction) compared to simple quinones. These facts together with remarkable photochemical behaviour of one of the quinone-tailed porphyrins (3) suggest these intramolecular complexes to be potential non-biological models for a synthetic approach to photosynthesis.

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Note added in proof

Since the submission of this manuscript, reports have appeared about a quinone-tailed porphyrin in which two types of quinones are linked to an etioporphyrin (Nishitani *et al* 1983) and a tetraphenyl porphyrin covalently linked to both a carotenoid and a quinone (Moore *et al* 1984). In the latter molecule excitation of the porphyrin moiety by visible light results in rapid formation of Carotene⁺—porphyrin-quinone⁻ as transient species with unfavourable recombination of charges similar to *in vivo* photosynthesis. A cofacial porphyrin-quinone molecule of a tetraphenyl type has also been reported (Lindsey and Mauzerall, 1982).

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Alkaloids from Indian medicinal plants and their biosynthesis

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Abstract. The chemical, pharmacological and biosynthetic status of alkaloids from plants which either have a reputation in folklore medicine or the extracts of which have shown consistent biological activity in a broad biological screen has been reviewed.

Keywords. Medicinal plants; alkaloids; biological activity; synthesis; biosynthesis.

1. Introduction

Alkaloids occupy a unique place in the family of natural products and provide challenging problems for structural elucidation, synthetic and biosynthetic studies. Recognising the importance of alkaloids and alkaloid biosynthesis coupled with our interest in biologically active natural products, we initiated some 15 years ago, at the Central Drug Research Institute, Lucknow, a study of various aspects of alkaloids of Indian plants which either show a consistent biological activity when screened or have a reputation in folklore medicine. The results of chemical, pharmacological and biosynthetic studies carried out on alkaloids from these plants have been reviewed.

2. Alkaloids from medicinal plants

A search for hypotensive agents in the active alkaloidal fraction of the alcoholic extract of the leaves and stems of *C. sparsiflorus* (Euphorbiaceae) (Bhakuni *et al* 1969), a South American plant which has now completely naturalised and grows as a weed in the plains of India, led to the isolation of proaporphines, crotsparine (1) (Bhakuni and Dhar 1968), N-methylcrotsparine (2), N,O-dimethylcrotsparine (3), dihydroproaporphine, crotsparinine (4) (Bhakuni and Dhar 1969) and the known aporphine, sparsiflorine (6) (Chatterjee *et al* 1965). The structures and stereochemistries of the new bases have been assigned (Bhakuni *et al* 1970b).

Proaporphines (Stuart and Cava 1968) are important biogenetic precursors of aporphines and the latter are also obtained chemically from proaporphines by the dienone-phenol and dienone-benzene rearrangements (Barton and Cohen 1957). The absolute configuration of proaporphines has been assigned with the aid of CD data (Snatzke and Wollenberg 1966) and by comparison of the optical rotation of dienone bases and the corresponding aporphines and also by chemical degradation procedure (Cava *et al* 1964a/b). The absolute configurations of the proaporphine alkaloids of *C. sparsiflorus* have been determined by direct synthesis from 1-benzyltetrahydroisoquinolines (Bhakuni *et al* 1972a/b).

Crotoflorine (Chatterjee and Majumdar 1968) and jacularine (Stuart *et al* 1968)

respectively, are most probably identical with the acetate of crotsparine and crotsparinine respectively.

Crotsparine (1), N-methylcrotsparine and N-methylcrotsparinine are hypotensive agents (Dubey *et al* 1969). N-Methylcrotsparinine (5) produces a sharp but shortlived fall in blood pressure which could be antagonised by atropine to a large extent suggesting thus a cholinergic mechanism of action. N-Methylsparsiflorine methiodide is a potent neuromuscular blocking agent. At 5 to 10 mg/kg (i.v.) in cats it produces 100% blockage of neuromuscular transmission for 30 to 60 min. Glaziovine, an enantiomer of (S)-N-methylcrotsparine, is a potent tranquillizer devoid of depressant effects.

In a routine biological screening a 50% ethanolic extract of *Cocculus pendulus* Diels. (Menispermaceae), a shrub that grows in dry parts of North and Western India, showed hypotensive and anticancer activities (Bhakuni *et al* 1969). A detailed chemical investigation of the active fraction of the ethanolic extract furnished six bisbenzylisoquinolines, pendulin (Gupta *et al* 1970), cocsolin (Joshi *et al* 1974), cocsulin (Bhakuni *et al* 1970), cocsulinin (Joshi *et al* 1974), pendulinin and pendin. Of these bases pendulin (7) showed hypotensive activity and cocsulinin (8) was found active against cells derived from human carcinoma of the nasopharynx (9 KB). An account of chemical work leading to the assignment of the structures and stereochemistries of new bases of *C. pendulus* has been reported (Bhakuni and Joshi 1975).

Cocculus laurifolius DC. (Menispermaceae), an ever green shrub grows in tropical and subtropical regions of the world. A 50% ethanolic extract of the leaves when tested hypotensive and neuromuscular activities were confirmed (Bhakuni and Dhar 1969). A systematic study of the active fraction of the alcoholic extract led to the isolation of ten new abnormal *Erythrina* alkaloids, isococculidine (12) (Bhakuni *et al* 1976), isococculine (13) (Singh *et al* 1978), coccupine (14) (Singh *et al* 1976), coccupinine (15) (Singh and Bhakuni 1977), cocculitine (16) (Singh *et al* 1977), cocculitinine (17), cocculidinone (18), cocculimine (20), coccludienone (19), coccoline (21) and coccolinine (22) (Pande *et al* 1976) and three new dibenz[*d,f*] azonines, laurifonine (24), laurifine (25) and laurifinine (26) (Pande and Bhakuni 1976). In addition to these new bases known morphinan-dienone alkaloid, sebiferine (23) (Sivakumaran and Gopinath 1976); two proaporphines, stepharine (27) and N-methylstepharine (28) (Cava *et al* 1964); five quaternary aporphines, magnoflorine, laurifoline, chlorides, isocorydine, O-methylisocorydine and boldine methochlorides and benzylisoquinolines, coclaurine, N-methylcoclaurine, reticuline, and laudanidine have also been isolated. The structures and stereochemistries of the new abnormal *Erythrina* alkaloids and dibenz [*d,f*] azonine bases have been determined (Bhakuni and Jain 1980).

Isococculidine (12), the major alkaloid of the leaves of *C. laurifolius* has been found to have neuromuscular blocking and hypotensive activities (Kar *et al* 1976), cocculidine (10) and cocculine (9) exhibit hypotensive activity. This activity in these alkaloids has been found due to ganglionic blocking action. The quaternary aporphines, O-methylisocorydine, isocorydine, and boldine methochlorides exhibit *d*-tubocurarine like curarising action on sciatic skeletal muscles. These quaternary bases also induce hypotensive effects in dogs, cats and rabbits. This activity has been found due to considerable ganglionic blocking action on various sympathetic and para-sympathetic ganglia.

Extracts of the roots of *Thalictrum foliolosum* DC (Ranunculaceae), a tall perennial herb, are used by the natives for the treatment of many ailments. A 50% ethanolic extract of the plant when screened, spasmolytic activity was confirmed (Dhawan *et al*

1980). A systematic chemical study of the active fraction of the alcoholic extract gave a new aporphine, N,O,O-trimethylsparsiflorine and known bisbenzylisoquinolines, (Chatterjee *et al* 1952; Gopinath *et al* 1959; Vashishtha *et al* 1941) thalidasine and thalrugosidine, benzylisoquinoline-aporphine base, thalicarpine, benzylisoquinoline, reticuline, berberine bases, berberine and palmatine and quaternary aporphine, magnoflorine (Bhakuni and Singh 1982). Of these bases thalicarpine (29) (Shamma and Rothenberg 1978) produces transient hypotensive effects in cats and exhibits significant inhibitory activity against Walker carcinosarcoma 256 in rats. Thalrugosidine (31) (Shamma *et al* 1967) exhibits antimicrobial activity. Thalidasine (30) (Kupchan *et al* 1967) has significant inhibitory activity against Walker intramuscular carcinosarcoma 256 in rats. The base also shows hypotensive and antimicrobial activities. Berberine and palmatine exhibit antimicrobial activity against a wide variety of micro-organisms including fungi and protozoa (Amin *et al* 1969). Berberine in addition shows cytotoxic and neoplasm inhibitory effects against tumor cells. The base markedly inhibits acetylcholinesterase both *in vivo* and *in vitro* thereby causing temporary decrease of blood pressure. Magnoflorine exhibits marked hypotensive activity. Thalidasine, thalicarpine, thalrugosidine, and N,O,O-trimethylsparsiflorine have been screened for antibacterial and antifungal activities and found to be inactive (Srivastava 1982).

About 250 *Corydalis* species occur in the Himalayan region and Khasi hills. *C. meifolia*, a perennial herb with underground tubers, is one of these species and grows at an altitude of 12000 to 15000 feet. Extracts of many *Corydalis* species are reported to be efficacious in many ailments in the Ayurvedic system of medicine. Ochotensine, an alkaloid that occurs in many of these species, has been reported to stimulate isolated guinea pig and rabbit uterus and induces a fall in blood pressure in anaesthetised cats.

Although a number of *Corydalis* species have been investigated and a variety of 1-benzylisoquinoline derived alkaloids have been isolated, *C. meifolia* wall appeared to have escaped the attention of chemists and pharmacologists. The plant was, therefore, collected from Kedarnath, UP, India. A 50% ethanolic extract of the plant material was prepared, screened and spasmolytic activity was confirmed in the extract (Dhawan *et al* 1980). Careful chromatography of the active fraction on silica gel gave six tetrahydroprotoberberines, (+)-sinactine, apocavidine, stylophine, (+)-cavidine, cheilanthifoline, and dehydrocavidine, two spirobenzylisoquinolines, yenusomine and yenusomidine, one phthalideisoquinoline, corlumine, one benzophenanthridine, dihydrosanguinarine and protopine (Bhakuni and Chaturvedi 1983). Of the isolated bases, dehydrocavidine is a new base. The remaining alkaloids, although known, have been isolated for the first time from the plant. A number of alkaloids isolated from *C. meifolia* exhibit biological activity. Corlumine is used as convulsant. Subconvulsive doses of the base increase the frequency and depth of respiration. The base has little effect on profused frog heart. Its effects on isolated intestine and uterus are irregular. Protopine has an inhibiting action on isolated frog heart muscles or nerve and a stimulating action on guinea pig intestine. The base has been screened against transplant hard mouse tumor sarcoma 180 and Ehrlich mouse carcinoma. Inhibition of tumor induced by protopine was significant and associated with considerable cytotoxic side effects. Protopine when injected intravenously in rabbits and guinea pigs, exerts a moderate pressor effects and sensitized the animal to induction of cardiac arrhythmias by adrenalina. In small doses the base has a narcotic action in frog, while large doses abolish reflex activity and show a curare like action. Large doses (18 mg to 200 mg/kg) when given parenterally to

is an analgesic and hypotensive. Cavidine, protopine, coramine, yemusoline and dehydrocavidine have shown moderate to high order of spasmolytic activity (Patnaik 1983).

C. cornuta and *Dicentra macrocapnos* Prain. (Papaveraceae) have good reputation in folklore medicine. These plants were, however, not investigated chemically. These were, therefore, collected from the Himalayan region from an altitude of 7000 to 8000 feet. Chemical examination of these furnished (–)-stylophine, protopine and (–)-coreximine (Jain and Bhakuni 1977). *C. govaniana* wall., a perennial herb with bright yellow flowers, grows in the Western Himalayas at an altitude of 2500 to 4000 metres, was yet another important medicinal plant. Systematic chemical investigation of the plant has given three new protoberberines, govadine (Mehra *et al* 1976), govanine (Mehra *et al* 1976), corygoanine and a known phthalideisoquinoline base, bicucculine. The structures of the new bases have been assigned (Mehra *et al* 1976).

Extracts of the rhizomes of *Stephania glabra* Miers. (Menispermaceae), a glabrous climber indigenous to the lower Himalayas (5000 to 6000 feet) have long been used by the natives as antidiysenteric, antipyretic and antiasthmatic. A 50 % ethanolic extract of the rhizome when screened, hypotensive and spasmolytic activities were confirmed in the extract (Dhar *et al* 1968). A search for active principles in the active fraction led to the isolation of two bisbenzylisoquinolines, cycleanine and N-desmethyleycleanine, five tetrahydropprotoberberines, capaurine, corynoxidine, tetrahydropalmatine, corydalmine and stepholidine, two proaporphines, stepharine and pronuciferine and four quaternary protoberberine salts, palmatine, dehydrocorydalmine, jatrorrhizine and stepharanine (Bhakuni and Gupta 1982). Many of these alkaloids exhibit biological activity. Tetrahydropalmatine hydrochloride causes hyperthermia in rats. Palmatine has been found to possess ACTH-like bactericidal and anticholinesterase effects. It has been concluded that palmatine, dl-tetrahydropalmatine and ergot alkaloids have an analogous pharmacological mechanism. Stepharine has been reported to have antihypertensive properties. Cycleanine is an antitumor agent. Structure activity relationship has been studied in capaurine for emetine type activity. pronuciferine hydrochloride shows good spasmolytic activity. There was 75 % blockage at a dose of 25 microgram when tested on the tissue ileum of guinea pig.

S. elegans is yet another interesting medicinal plant which has not been investigated chemically. The plant was, therefore, collected from Dehradun and systematic investigation resulted in the isolation of epihernandolinol, N-methylcorydalmine, hasubanonin, aknadinin, cyclanoline, magnoflorine, isotetrandrine, isochondodendrine and cycleanine (Singh *et al* 1981). Many of these alkaloids are well known for their biological activities.

Several species of *Litsea* (Lauraceae) are found in India. Extracts of many of these species are reported efficacious in the treatment of various ailments. A 50 % ethanolic extract of *L. glutinosa* var. *glabraria* exhibited spasmolytic activity (Bhakuni *et al* 1969). The extract of *L. wightiana* showed significant spasmolytic, hypothermic and blood pressure lowering activities (Dhar *et al* 1974). Investigations of the biologically active fraction of the alcoholic extract have yielded six aporphines, norboldine, boldine, laurotetanine, N-methyl-laurotetanine, actinodaphnine, and N-methylactinodaphnine (Tewari *et al* 1972). Glaucine, boldine, norboldine, isoboldine, norcorydine and laurotetanine have been obtained from *L. wightiana* (Bhakuni and Gupta 1983). From

L. sebifera, boldine, laurotetanine and actinodaphnine have been isolated (Uprety *et al* 1972). The alkaloidal constituents of *Actinodaphne obovata* Bl., collected from Eastern Himalayas and Assam have also been investigated and aporphines, laurotetanine, N-methylaurotetanine, and actinodaphnine have been isolated (Bhakuni *et al* 1972).

A 50% ethanolic extract of the leaves of *Annona squamosa* L. (Annonaceae), a small evergreen tree which grows wild and is also cultivated throughout India for its fruits, exhibited anticancer activity. Search for active principles led to the isolation of corydine, a base reported to have anticancer activity and six other aporphines, anonaine, roemerine, norcorydine, norisocorydine, isocorydine and glaucine (Bhakuni *et al* 1972). Of these alkaloids glaucine is reported to cause narcosis in animals. Boldine has sedative properties. It is a cardiotonic and its toxicity is quite low, Glaucine and laurotetanine increase antimitotic effects of colchicine. The occurrence of anonaine, norlaureline, glaucine, corydine and isocorydine in *A. squamosa* is of biosynthetic interest.

Alangium lamarckii Thw. (Alangiaceae), *Senecio tenuifolius* Burm. (Compositae), *Retanilla ephedra* Brogn. (Rhamnaceae), *Aristotelia chilensis* (Eleocarpaceae) and *Discaria crenata* (Rhamnaceae) all are respectable plants in folklore medicine. The alkaloidal constituents of these plants have been investigated. Two new indole alkaloids, alangimarckine and ankorine have been isolated from *A. lamarckii* (Battersby *et al* 1966). The occurrence of dihydroprotoemetine with tubulosine and deoxytubulosine in *A. lamarckii* is of considerable biosynthetic interest and this holds also for ankorine and alangimarckine. Four macrocyclic diester pyrrolizidine alkaloids, sencionine, senkirkine, O-acetylsenkirkine, and integerrimine have been obtained from the leaves and stems of *S. tenuifolius* (Bhakuni and Gupta 1982). Senecionine and integerrimine generally co-occur in *Senecio* species. These bases are, however, present in *S. tenuifolius* as minor constituents only. Integerrimine is an ester of integerrineic acid whereas senecionine is the ester of the *trans*- isomer, senecic acid. From the roots of *R. ephedra*, the peptide alkaloids, integerresine and crenatine A, the aporphines, boldine and norboldine and the benzylisoquinolines, armepavine, norarmepavine, coclaurine and N-methylcoclaurine have been isolated (Bhakuni *et al* 1974). The unusual indole alkaloids, aristoteline and aristotelone have been obtained from *Aristotelia chilensis* (Bhakuni *et al* 1970).

3. Synthesis of alkaloids

(+)-Ophiocarpine, a minor alkaloid of the leaves and stems of *Cocculus pendulus* Diels, has been assigned the structure and configuration as shown in 32. A synthesis of ($\pm$)-ophiocarpine from berberine has been achieved (Bhakuni *et al* 1982). Antofine (33) and alkaloid C (34) are important phenanthroindolizidine alkaloids. These bases have been synthesized from 2-(3-hydroxy-4-methoxyphenyl)-1,6,7,8,8a-pentahydro-3-(4-hydroxyphenyl)-indolizin-4-one (Bhakuni *et al* 1982). Laurifonine (24), a dibenz [*d,f*]azonine alkaloid isolated from *Cocculus laurifolius* has been prepared from 4,4',5-trimethoxy-2,2'-biphenylaldehyde (Bhakuni and Mangla 1981). A biogenetic type synthesis of the phenanthroindolizidine alkaloid, tylophorine, has been reported (Mangla and Bhakuni 1980).

Tetrahydroprotoberberines, scoulerine, coreximine, tetrahydropalmatine and related compounds are of considerable biosynthetic interest. 1-Bromoscoulerine, 1,12-

dibromo scoulerine, 1-bromotetrahydropalmatine and 1,12-dibromotetrahydropalmatine and the corresponding mono- and dibromoreticuline derivatives could be utilised for 'aberrant biosynthesis'. ($\pm$)-Scoulerine, tetrahydropalmatine, coreximine and their 1-bromo- and 1,12-dibromo- derivatives have been synthesized by Mannich condensation of the 1-benzyltetrahydroisoquinolines with formaldehyde, using bromine as a protective group (Bhakuni and Kumar 1983). A convenient synthesis of septicine, a secophenanthroindolizidine alkaloid, has been developed (Mangla and Bhakuni 1980).

4. Biosynthesis of alkaloids

Reticuline (35), the putative precursor of a large number of 1-benzylisoquinoline derived alkaloids (Bhakuni 1976) is a good model to study some of the aspects of early stages of the biosynthesis of 1-benzylisoquinoline derived alkaloids. Since 1910 it has been believed that dopa gives rise to both the 'halves' of norlaudanosoline from which reticuline could be derived in Nature. Feeding experiments revealed that dopa in fact contributes only to the formation of the phenethylamine part of reticuline in *Litsea glutinosa* and the benzylic portion is biosynthesized from 3,4-dihydroxyphenylpyruvic acid not derived from dopa. This is a most surprising result (Tewari *et al* 1975). Other aspects of the biosynthesis of reticuline have also been studied and it has been demonstrated that trihydroxylated 1-benzyltetrahydroisoquinolines are not the precursor of reticuline. There is no specificity of O-methylation in the biosynthesis of reticuline. However, N-methylation of norreticuline is a specific process. Feeding experiments suggest that O-methylation precedes N-methylation in the biosynthesis of reticuline (Bhakuni *et al* 1977).

Coclaurine (36) is an established precursor of proaporphine, aporphine and bisbenzylisoquinoline alkaloids (Bhakuni 1976). Feedings of tyrosine, tyramine, dopa, dopamine and 4-hydroxyphenylpyruvic acid in *Annona reticulata* revealed that while tyramine, dopa and dopamine contribute to the formation of the phenethylamine portion of coclaurine, tyrosine and 4-hydroxypyruvic acid are incorporated into both halves. Tracer experiments have shown that coclaurine is biosynthesized *via* the intermediacy of nor-coclaurine-1-carboxylic acid, 1,2-didehydronorcoclaurine and norcoclaurine (Prakash *et al* 1979).

Papaverine (37), one of the major 1-benzylisoquinoline alkaloids of *Papaver somniferum* is clinically used as an antispasmodic agent. The main effect of papaverine hydrochloride is relaxation of smooth muscles. Papaverine has been shown to be biosynthesized in *P. somniferum* from two units of tyrosine *via* norlaudanosoline and nor-reticuline. The dehydrogenation of the 1-benzyltetrahydroisoquinoline precursor is an important step in the biosynthesis of papaverine. The mechanism of this reaction could be step-wise or it could proceed in a concerted manner. Further, this process could occur in a partially methylated 1-benzyltetrahydroisoquinoline precursor, such as nor-reticuline or it could take place in a completely methylated derivative such as norlaudanosine. The efficient incorporation of ($\pm$)-norlaudanosine into papaverine when coupled with the earlier data that 1,2-dehydroreticuline did not participate in the biosynthesis of papaverine clearly demonstrated that the dehydrogenation step occurs

partial O-methylation of nor-reticuline at C-7 or C3' could give rise to norlaudanidine or norcodamine respectively. Norlaudanosine can then of course be reached from both of these isomers by further O-methylation. However, when norcodamine and norlaudanidine were fed in parallel experiments to *P. somniferum*, the former was incorporated 10 times less efficiently than the latter, suggesting strongly that norlaudanidine is an intermediate between nor-reticuline and norlaudanosine. Parallel feeding experiments with reticuline and norreticuline demonstrated that N-demethylation of reticuline is not a favoured process in the biosynthesis. Although papaverine does not possess an asymmetric centre, yet enzymatic reactions are generally stereospecific and one can expect that either of the enantiomers of norreticuline would be the biological precursor of papaverine. (-) and (+)-, nor-reticulines when fed, papaverine was exclusively biosynthesized from (-)-norreticuline (Uprety *et al* 1975).

According to the most accepted biogenetic theory (Barton and Cohen 1957), oxidative cyclisation of coclaurine (36) could give rise to proaporphine alkaloid, crotsparine (1). The dihydroproaporphine, crotsparinine (4) could be formed by reduction of one of the double bond of crotsparine type intermediate and the aporphine alkaloid, sparsiflorine (6) would arise from crotsparine by dienone-phenol rearrangement. It has been demonstrated by feeding labelled ($\pm$)-coclaurine, ($\pm$)-isococlaurine and ($\pm$)-norcoclaurine to *Croton sparsiflorus* plants that crotsparine, dihydrocrotsparine and sparsiflorine are specifically biosynthesized from ($\pm$)-coclaurine. The presence of this key intermediate in *C. sparsiflorus* has been confirmed by trapping experiments (Bhakuni *et al* 1974). Crotsparine and crotsparinine have opposite configuration while sparsiflorine and crotsparine have the same configuration at the corresponding asymmetric centres. If crotsparine is a biological precursor of crotsparinine, a change in configuration should occur at position C-6a in the isoquinoline moiety of the proaporphine during the course of biochemical transformations. Alternately crotsparine and crotsparinine could be biosynthesized by independent routes. Tracer experiments have confirmed that the latter route is followed in the biosynthesis of these bases. The biosynthesis of N-methylcrotsparine, N-methylcrotsparinine and N-methylsparsiflorine have been studied in detail and results have been reported (Bhakuni and Jain 1981).

The biosynthesis of yet another proaporphine alkaloid (Haynes *et al* 1965), crotonosine (45) has also been studied. Tracer experiments with ($\pm$)-, (+)- and (-)-, coclaurines demonstrated specific incorporation of (+)-isomer into crotonosine, isomeric ($\pm$)-isococlaurine was not a precursor of the base although ($\pm$)-norcoclaurine was incorporated. The evidence obtained has supported the view that oxidative cyclisation of (+)-coclaurine to a dienone is involved. Double labelling experiments involving the methoxy group of ($\pm$)-coclaurine showed that most but not all, the methoxy activity was lost in conversion into crotonosine (Barton *et al* 1967).

Boldine (38), the choleric principle of *Peumus boldus* Molina, is an attractive model to verify some of the current views on the biosynthesis of aporphine alkaloids. The incorporation of ($\pm$)-norprotosinomenine, ($\pm$)-nororientaline, ($\pm$)-norreticuline, ($\pm$)-, (-)-, and (+)-, reticulines into boldine in *Litsea glutinosa* have been studied. Specific utilization of (+)-reticuline into boldine has been demonstrated (Tewari *et al* 1974). The evidence supports the direct oxidative coupling of (+)-reticuline to

of the methoxy activity is lost in conversion into boldine (Bhakuni *et al* 1977).

Two biosynthetic pathways have been reported for the formation of 1,2,10,11-tetrasubstituted aporphine alkaloids. In one of the pathways direct *ortho-ortho* oxidative coupling of reticuline is involved to provide bulbocapnine and magnoflorine types of aporphine bases, while the second pathway makes use of neoproaporphine intermediate to furnish corydine types of compounds. The biosynthesis of isocorydine (39) could be envisaged both from reticuline and protosinomenine. In the third scheme the required isocorydine skeleton could also be generated from orientaline *via* a dienone. Feeding of labelled ($\pm$)-nororientaline in parallel with ($\pm$)-norprotosinomenine and ($\pm$)-reticuline established that isocorydine (39) is exclusively and specifically biosynthesized in *Annona squamosa* Linn. plants from reticuline. Feeding with ($\pm$)-norlaudanine demonstrated that it is a poor precursor of isocorydine. Feeding with labelled (+)- and (-)-norreticulines showed that stereospecificity is maintained in the conversion of 1-benzyltetrahydroisoquinoline into isocorydine (Prakash *et al* 1978).

The quaternary aporphine alkaloids, magnoflorine (41) and laurifoline (40), well known for their curarizing and hypotensive properties, could form in Nature from 1-benzyltetrahydroisoquinoline precursors by alternate biosynthetic routes. Feeding of labelled 1-benzyl-tetrahydroisoquinoline precursors revealed that magnoflorine and laurifoline in *Cocculus laurifolius* are biosynthesized from reticuline.

Parallel feedings with (S)-, and (R)-, reticulines demonstrated that the bases are stereospecifically formed in the plants from (S)-reticuline (Bhakuni *et al* 1980).

Biogenetic theory (Barton and Cohen 1957) suggests that the so-called 'abnormal aporphine alkaloids' lacking an oxygen substituent in ring D are derived from 1-benzylisoquinoline by oxidation to a dienone, reduction to dienol and dehydration with rearrangement to the fully aromatic compound. Using labelled precursors the relationship between the 1-benzylisoquinoline alkaloid, coclaurine and the aporphine alkaloid, roemerine (44) in *Papaver dubium* L. has been studied (Barton *et al* 1966). Various congeners of coclaurine have been used in the investigation of this biosynthesis. The corresponding biosynthesis of anonaine (43) in *Annona reticulata* L. has also been studied. The biosynthesis of mecambaine (42) has been more briefly investigated. The relationship between mecambaine and roemerine has been demonstrated. The results as a whole provide good support for the hypothesis that aporphine alkaloids of the anonaine-roemerine type are derived from coclaurine type precursors through phenol oxidation. Dienone of the crotonosine (45), mecambaine (42) types are intermediate (Barton *et al* 1967).

According to biogenetic theory (Barton and Cohen 1957), the abnormal aporphine alkaloid, nornuciferine-1 (46) could be biosynthesized from coclaurine derivatives. Tracer experiments in *Croton sparsiflorus* with ($\pm$)-norcoclaurine, coclaurine and N-methylcoclaurine demonstrated that N-methylcoclaurine is specifically incorporated into nornuciferine-1. The evidence supports direct oxidative coupling of (+)-(S)-N-methylcoclaurine to give N-methylcrotsparine which in turn is shown to be a specific precursor of nornuciferine-1. The experiments also showed that N-methylcrotsparine is reduced to N-methylcrotsparinol which is then preferentially dehydrated and rearranged to nornuciferine-1 (Bhakuni *et al* 1979).

Sebiferine (23), a morphinandienone alkaloid could be biosynthesized from suitably substituted 1-benzyltetrahydroisoquinoline precursors through alternate biosynthetic

specifically biosynthesized from reticuline. A double labelling experiment involving the 4'-O-methyl group of ($\pm$)-norreticuline showed that the methoxy group is retained in the bioconversion of the precursor into sebiferine. There was, however, considerable loss of the tritium at C-1. Parallel experiments with (+)- and (-)-reticulines showed that the stereospecificity is not maintained in the biosynthesis of sebiferine from 1-benzylisoquinoline precursors. Feeding experiments also demonstrated that the enzyme system present in plants can efficiently convert flavinantine into sebiferine (Bhakuni *et al* 1978).

Stereochemical aspects related to the biosynthesis of the morphine alkaloids have been studied. Ozonolysis of tritiated salutaridiols-I and II, the biosynthetic intermediates of morphine alkaloids, has afforded glyceric acids whose absolute configurations have been determined by the isotope dilution method. The stereochemistry of salutaridinol-I, thus has been defined unambiguously. Oxidation of tritiated (+)- and (-)-reticulines followed by isotopic dilution analysis, has confirmed the configurational relationship between morphine and benzylisoquinoline alkaloids. Further support for this has been obtained by the reductive fission of salutaridine to give after appropriate methylation, (-)-laudanidine. The bond cleaved in this reduction is the bond formed in the biogenetic oxidation of (-)-reticuline (Barton *et al* 1967).

Phenanthroindolizidine alkaloids tylophorine (47) and tylophorinine (48) (Govindachari *et al* 1954) exhibit wide range of biological activities and provide fascinating problem for biosynthetic studies. Tracer experiments (Mulchandani *et al* 1969, 1971) revealed that ring A and carbon atoms C₁₀ and C₆' and ring B and carbon atoms C₉ and C₇, of tylophorine in *Tylophora asthmatica* are derived from phenylalanine and tyrosine respectively. Ornithine is also incorporated, thus suggesting its participation in tylophorine biosynthesis *via* Δ^1 -pyrrole. Late stages of biosynthesis of tylophorine and tylophorinine have also been studied with labelled substituted 6,7-diphenylhexahydroindolizines and a trisubstituted compound has been shown as an intermediate (Herbert and Jackson 1977). We disagreed with this and re-examined the biosynthesis of these alkaloids. Initially administration of 3,4-dihydroxyphenylalanine (dopa) to young *T. asthmatica* plants showed that ring B and carbon atoms C₉ and C₇' of tylophorine and tylophorinine are derived specifically from dopa. Experiments with ¹⁴C and ³H labelled 6,7-diphenylhexahydroindolizines demonstrated that both the alkaloids in *T. asthmatica* are biosynthesized from 6-(3-hydroxy-4-methoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-1,2,3,5,7,8a-hexahydroindolizine (Bhakuni and Mangla 1981).

Aristolochic acid (49), a representative of the substituted 10-nitrophenanthrene-1-acids which occurs in many species of the genus *Aristolochia* and several other members of the family Aristolochiaceae, is a potent tumor inhibitor. Biogenetically it is considered to be derived from 1-benzyltetrahydroisoquinoline precursors *via* aporphine intermediates. The incorporation of tyrosine, dopa, nororientaline, orientaline, prestepharine and stepharine into aristolochic acid in *Aristolochia bracteata* has been studied. Specific incorporation of nororientaline has been demonstrated. The evidence

Laurifinine (26), a typical representative of trisubstituted dibenz $[d,f]$ azonine alkaloids isolated by us from the leaves of *Cocculus laurifolius* could be formed in nature from N-norprotosinomenine, an established precursor of *Erythrina* alkaloids (Barton *et al* 1968). Para-Para oxidative coupling of norprotosinomenine could give neoproaporphine, which on reduction followed by elimination and rearrangement would furnish dibenz $[d,f]$ azonine skeleton. Reduction of imine followed by N-methylation could finally yield laurifinine. Labelled tyrosine was initially fed to young cut branches of *C. laurifolius* and it was found that the plants were actively biosynthesising laurifinine. In subsequent experiments the theoretical precursors of laurifinine such as nor protosinomenine, nororientaline, norreticuline and N-[2-(3-hydroxy-4-methoxyphenyl)-ethyl]-2-(4'-hydroxyphenyl) ethylamine when were fed, it was found that only norprotosinomeine was efficiently metabolized by the plants to form laurifinine. Intact incorporation of norprotosinomenine into laurifinine was demonstrated by double labelling experiments with $(\pm)$ -[1- ^3H , 4'-methoxy- ^{14}C], and [1- ^3H , 7-methoxy- ^{14}C]N-norprotosinomenines. In both the experiments $^3\text{H}:^{14}\text{C}$ ratios in the precursors and the product were essentially the same. The experiments further showed that 4' and 7- OMe groups and the hydrogen atom at the asymmetric centre of the precursor are retained in the bioconversion into laurifinine. Parallel experiments with (+)- and (-)-N-norprotosinomenines demonstrated specific utilisation of (+)-isomer into laurifinine (Bhakuni and Jain 1981).

Cocculidine (10) and cocculine (9), the hypotensive principles of *Cocculus laurifolius* and are representative of abnormal *Erythrina* alkaloids. These bases could be formed in nature from norprotosinomenine. In the bioconversion, one of the oxygen function of the precursor could be eliminated by dienone-benzene rearrangement. However, the possibilities of the formation of these abnormal *Erythrina* alkaloids from other 1-benzyltetrahydroisoquinolines such as norreticuline and nororientaline and from the suitably substituted N-phenethylamine could not be ruled out (Barton *et al* 1974). The incorporation of labelled $(\pm)$ -, N-norprotosinomeine, N-norreticuline, N-nororientaline and N-[2-(3-hydroxy-4-methoxyphenyl) ethyl]-2-(4'-hydroxyphenyl) ethylamine into cocculidine and cocculine in *C. laurifolius* were studied and specific utilisation of N-norprotosinomenine into the alkaloids demonstrated. Feeding of protosinomenine revealed that the plants do not have the ability to carry out selective N-demethylation to give N-norprotosinomenine. A double labelling experiment with $(\pm)$ -[1- ^3H , 4'-methoxy- ^{14}C]N-norprotosinomenine showed that the 4'-O-methoxy group of the precursor is retained in the bioconversion and the erythrinan ring system is not formed by addition of the secondary amino function onto an orthoquinone system. Parallel experiments with (+)- and (-)-N-norprotosinomenines demonstrated specific incorporation of (+)-isomer into cocculidine. High incorporation of cocculidine into cocculine revealed that O-demethylation is the terminal step in the biosynthesis of cocculine. Feeding experiments also showed that the plants can convert isococculidine into cocculidine with very high efficiency. N-norprotosinomenine has been specifically incorporated into cocculidine and cocculine, its presence in *C. laurifolius* has been shown by trapping experiments. N-Norprotosinomenine is thus a true biological precursor of the abnormal *Erythrina* alkaloids (Bhakuni and Singh 1978).

Tetrahydropalmatine and palmatine, isolated from *Stephania glabra* are representatives of protoberberine alkaloids. These bases occur in nature either as tetrahydropro-

berberines or quaternary protoberberine salts. Tetrahydroprotoberberines are also important intermediates in the biosynthesis of a large number of 1-benzyltetrahydroquinoline derived alkaloids (Bhakuni 1976). Recent tracer experiments have shown that tetrahydroprotoberberine alkaloids give rise in nature to benzophenanthridine, pirobenzylisoquinoline, protopine, phthalideisoquinoline, rheadine and retroproberberine alkaloids. A biogenetic connection between the benzylisoquinoline and berberine group of alkaloids (Robinson 1955) recognised quite early has been firmly confirmed by tracer experiments (Gear and Spenser 1963; Batterby *et al* 1963; Gupta and Spenser 1965 and Skerl and Gros 1971). Further it has been demonstrated that C atom 8 of berberine group of alkaloids is derived from the N-Me group of 1-benzylisoquinoline precursors (Barton *et al* 1965 and Battersby *et al* 1965). Negligible incorporation of reticuline into tetrahydropalmatine in *Papaver somniferum* has been recorded (Brochman Hanssen *et al* 1971).

We re-examined the biosynthesis of tetrahydropalmatine and palmatine. Tyrosine was initially fed to young cut branches of *C. laurifolius* and young plants of *Cissampelos pariera* and it was found that plants in both cases were biosynthesising tetrahydropalmatine and palmatine. Incorporation of tyrosine into protoberberine alkaloids was, however, slightly higher in *C. laurifolius*. In subsequent experiments labelled hypothetical precursors were fed to young cut branches of *C. laurifolius* plants. Feeding of tyrosine in parallel with ($\pm$)-nororientaline, norprotosinomenine and norlaudanidine revealed that these 1-benzyltetrahydroisoquinoline derivatives are very poorly metabolised by the plants. Feeding with ($\pm$)-norlaudanoline and reticuline showed that these are efficient precursors of the bases. The completely methylated 1-benzyltetrahydroisoquinoline, ($\pm$)-laudanoline was not incorporated. Biosynthetic tetrahydropalmatine derived from ($\pm$)-[3- 14 C] reticuline was treated with methyl iodide which had essentially the same radioactivity as the parent base. The methiodide was converted into methoxide and then subjected to Hofmann degradation to give the methine-I with essentially no loss of radio activity. Ozonolysis of the methine-I gave radioactive formaldehyde (dimeedone derivative, 98 % of original activity). Biosynthetic palmatine derived from ($\pm$)-[3- 14 C] reticuline was reduced with Sn/HCl to give tetrahydropalmatine which had essentially the same radio activity as the parent base. It was then subjected to Hofmann degradation as above to give the corresponding methine which on ozonolysis afforded radio active formaldehyde (dimeedone derivative, 77 % of the original activity). The results thus established specific incorporation of reticuline into tetrahydropalmatine and palmatine. Reticuline was incorporated intact into tetrahydropalmatine was shown by double labelling experiment as follows: (+)-1- 3 H, 4'-Methoxy- 14 C] Reticuline was fed to the young cut branches of *C. laurifolius* and biosynthetic tetrahydropalmatine was isolated. The ratios of 14 C : 3 H was 1 : 38 and in the biosynthetic base 1 : 37. The C atoms 8 in tetrahydropalmatine and palmatine are formed by oxidative cyclisation of N-Me group of reticuline have been shown as follows. ($\pm$)-N-Methyl-[14 C] Reticuline was fed and biosynthetic bases of interest were isolated. Labelled palmatine was treated with phenylmagnesium bromide to give α -phenyldihydropalmatine. Chromic acid oxidation of the radioactive compound in the usual way (Kuhn-Roth) gave radioactive benzoic acid (102 % original activity). Biosynthetic tetrahydropalmatine derived from ($\pm$)-N-methyl-[14 C] reticuline was dehydrogenated to give radioactive palmatine which was degraded as above to give radioactive benzoic acid (98 % original activity). The foregoing experiments established

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laurifolius. The precursors used, however, were racemic. It would be expected that in the biotransformation only one of the two optical isomers should act as a direct substrate. Parallel feedings with (+)- and (-)- reticulines demonstrated that stereospecificity is maintained in the bioconversion of 1-benzyltetrahydroisoquinoline precursors into tetrahydropalmatine and palmatine. (+)-Reticuline was incorporated about 70 times more efficiently than the (-)-enantiomer. Feeding of labelled tetrahydropalmatine and palmatine showed that the former was very efficiently incorporated into the latter whereas the incorporation of the latter into former was practically negligible. (+)-Reticuline has been isolated from *C. laurifolius*. Its presence in the plants was again confirmed by feeding tyrosine. (+)-Reticuline is, thus, a true precursor of tetrahydropalmatine and palmatine. The foregoing experiments strongly support the following sequence for the biosynthesis of tetrahydropalmatine and palmatine in *C. laurifolius*. Tyrosine → norlaudanosoline → (+)-reticuline → tetrahydropalmatine → palmatine (Bhakuni *et al* 1980).

Several abnormal *Erythrina* alkaloids have been isolated by us from the leaves of *Cocculus laurifolius* (Bhakuni and Jain 1980). We have studied the early stages of biosynthesis of cocculidine, cocculine (Bhakuni and Singh 1978) and isococculidine (Bhakuni *et al* 1977) and have shown that these alkaloids are stereospecifically biosynthesized from (+)-(S)-norprotosinomenine. We have also examined the late stages of biosynthesis of these alkaloids and found that isococculidine in the plants is converted into cocculine *via* coccuvanine and isococculine into coccolinine *via* coccuvine (Bhakuni and Jain 1980).

5. Bisbenzylisoquinoline alkaloids

Bisbenzylisoquinoline alkaloids constitute the largest group of isoquinoline alkaloids and are distributed mostly among the members of Menispermaceae and Rannunculaceae families (Shamma 1972). Biogenetically bisbenzylisoquinoline alkaloids are considered to be formed in Nature by oxidative dimerisation of simple 1-benzyltetrahydroisoquinoline bases. Different sub-groups of bisbenzylisoquinoline alkaloids have been recognised due to availability of different sites for oxidative dimerisation. The members of the sub-group differ in the nature of the oxygenated substituents or the oxidation state or degree of substitution at the two nitrogen atoms or in stereochemistry at the two asymmetric centres. Based on these differences bisbenzylisoquinolines have been classified recently into twenty-six types (Shamma and Moniot (1976). We have studied the biosynthesis of representatives of several groups of bisbenzylisoquinoline alkaloids.

The simple bisbenzylisoquinoline, tetrandrine which affects the central nervous system, respiratory and skeletal muscles and is also an effective tumor inhibitor, has been shown to be formed in Nature by oxidative dimerisation of S-(+)-N-methylcocclaurine (Bhakuni *et al* 1980). The biosynthetic sequence of cocculinin, an anticancer agent of *Cocculus pendulus* (Bhakuni and Joshi 1975) have been traced (Bhakuni *et al* 1978). Oxyacanthine, the hypotensive principle of *Berberis vulgaris* Linn. and a representative of bisbenzylisoquinoline alkaloids containing two phenyl ether linkages have been shown to be formed in Nature by inter- and intra-molecular oxidative couplings of (S)- and (R)-N-methyl-cocclaurines (Bhakuni *et al* 1978).

have also been demonstrated to be biosynthesised from (S)- and (R)-,N-methylcoclaurines (Bhakuni *et al* 1980).

Biosynthesis, a tool for determining the structure and absolute configuration of alkaloids

Biosynthesis has been used as a tool for determining the structures and absolute configurations of alkaloids. Isomeric bases nortiliacorinine A and nortiliacorinine B have been isolated from *Tiliacora* species (Anjaneyulu *et al* 1969). The position of N-methyl group and the stereo-chemistries at the two asymmetric centres in these bases remained undefined. By using coclaurine derivatives the structure and absolute configuration of nortiliacorinine A has been defined (Bhakuni *et al* 1981).

The absolute configuration at the asymmetric centres C-1 and C-1' in the diastereoisomeric alkaloids tiliacorine and tiliacorinine cannot be determined by the usual sodium-ammonia cleavage method because the two lower rings of these bases are linked through a direct carbon-to-carbon bond, rather than through the much more common ether bridge. By tracer experiments it has been shown that tiliacorine has the S- and R-configuration at the asymmetric centres C-1 and C-1' respectively and tiliacorinine has the 'SS-' configuration at both centres (Bhakuni and Jain 1981; Bhakuni *et al* 1978). Absolute configuration of bisphenylbisbenzylisoquinoline alkaloid, tiliageine has also been similarly determined (Bhakuni and Singh 1978). Tumor inhibitory base, thalicarpine (29) which also possesses hypotensive activity, is a representative of aporphine-1-benzylisoquinoline alkaloids. Biogenetically thalicarpine is unique. It is one of the rare dimeric alkaloid which could derive in Nature from two reticuline units. The base could also be formed by oxidative coupling of reticuline and preformed aporphine of N-methylaurotetanine type. Using norlaudanosoline derivatives it has been established that thalicarpine is stereospecifically biosynthesised by oxidative coupling of (S)-reticuline. Feeding experiments also showed that the plants can convert (S)-boldine and (S)-isoboldine into thalicarpine (Bhakuni and Jain 1982). (+)-Sinactine is a tetrahydroprotoberberine alkaloid. The absolute configuration of the base has been determined by biosynthetic method (Bhakuni *et al* 1983).

Aberrant biosynthesis of unnatural alkaloids

We know very little about the potentiality of higher plants to carry out transformations of organic molecules which they do not normally produce or contain. These types of transformation where an 'unnatural precursor' is converted into an 'unnatural product' in a living system is called 'aberrant biosynthesis'. This area of research is relatively unexplored in higher plants. A few reported examples of aberrant biosyntheses are the conversion of 5-fluoronicotinic acid into 5-fluoronictinine in the tobacco plant *Nicotiana tabacum* (Leete *et al* 1971); and conversion of N-methyl- Δ^1 -piperidineinium chloride into higher homologue of nicotine (Leete and Chedekel 1972).

We have demonstrated bioconversion of 8-bromo- and 8,2'-dibromo- reticulines in *Locustulus laurifolius* into 1-bromo- and 1,12-dibromotetrahydropalmatine and also of 12-nitro and 2'-aminoreticulines into 12-nitro and 12-amino-tetrahydropalmatines. The experiments suggest that many of the enzymes in plants are non-specific and are able to

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Abstract. Microbial degradation of geraniol, citronellol, linalool and their corresponding acetates, structurally modified linalool and linalyl acetate, α -terpineol and β -myrcene are presented. Oxygenative and prototropic rearrangements are normally observed during the microbial metabolism of monoterpenes. Three types of oxygenation reactions are observed, namely, (a) allylic oxygenation (b) oxygenation on a double bond and (c) addition of water across the double bond. The studies indicate commonality in the reaction types or processes occurring during the metabolism of various related monoterpenes and also establish the convergence of degradative pathways at a central catabolic intermediate.

Keywords. Monoterpenes; micro-organisms; metabolism; prototropic-cyclization; oxygenation; fermentation; degradation; aromatization.

1. Introduction

Monoterpenes are widely distributed in nature and they are the usual constituents of essential oils. These natural products, mostly of higher plant origin, are subjected to oxidative metabolism by various types of micro-organisms present in the soil. This process of 'mineralization' is an essential biochemical step in the 'carbon cycle' occurring in nature. Terpenes, particularly the monoterpene alcohols due to their antimicrobial property are generally resistant to microbial degradation. However, during the course of evolution some of the saprophytic micro-organisms, especially the species belonging to *Pseudomonas* have acquired the unique ability to degrade and live on these compounds. In the process of utilizing these compounds as the carbon source, the micro-organisms carry out several interesting rearrangements in the molecule before ultimately degrading them to carbon dioxide and water. On the other hand, fungi is normally unable to degrade a terpene molecule all the way to carbon dioxide and water, although when grown in the presence of energy-rich medium, can metabolize or transform them due to the nonspecific nature of the enzymes present in them.

The unique ability of micro-organisms to carry out different types of reactions has attracted the attention of synthetic organic chemists. Microbes can serve as an important tool in the hands of the organic chemists. The most important aspect of microbes is their ability to catalyze reactions with high degree of stereospecificities. Microbes can introduce stereospecifically oxygen function, bring about the transformations of certain functional groups or carry out asymmetric hydrolysis, which may be either difficult or require a number of intermediate stages in a conventional approach. In fact micro-organisms are extensively used in the steroid transformations. Steroidal intermediates, which are difficult to synthesize are achieved by the use of microbial systems (Vezina and Singh 1976). One such example is the 11α -hydroxylation of progesterone by *A. ochraceus* or *R. nigricans* (Peterson and Murray 1952). Even the

Progress in the microbial degradation of terpenoids in general and monoterpenes in particular, lagged considerably behind as compared to the enormous amount of work carried out with regard to other classes of compounds such as steroids was mainly due to (a) the non-physiological character of terpenoids, and (b) their ability to inhibit the growth of diverse microbial flora. The first detailed work on the microbial degradation of acyclic monoterpenes has been reported in the early part of 1960 (Seubert *et al* 1963; Seubert and Remberger 1963; Seubert and Fass 1964). They have studied the metabolism of citronellal (1), citronellol (2), geraniol (3) and geranic acid (4) by a soil bacterium, *Pseudomonas citronellolis*. It has been observed that the metabolism of these acyclic monoterpenes is initiated by a step-wise oxidation of the primary alcoholic group to the carboxylic group, followed by carboxylation of the C-10 methyl group (β -methyl) by a biotin-dependent carboxylase. The carboxy methyl group gets eliminated at a later stage as acetic acid. Further degradation follows the β -oxidation pattern. On the basis of specificity of the enzyme geranyl carboxylase, it has been suggested that the pathways of degradation of citronellic (5), geranic (4) and neranic (6) acids converge at the neranic acid (Seubert and Fass 1964). The details of the pathway are shown in figure 1.

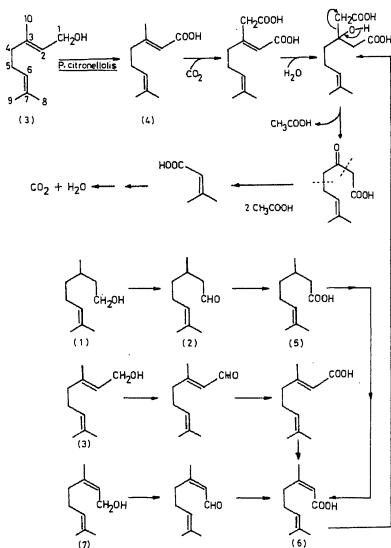
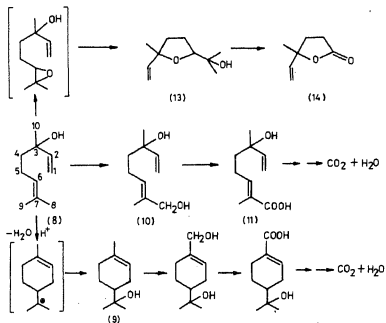


Figure 1. Pathways of degradation of geraniol, nerol and citronellol by *P. citronellolis*.

In contrast to the above findings, higher plants (Madyastha *et al* 1976), fungi (Madyastha and Murthi, Unpublished observation) and mammalian systems (Chadha and Madyastha 1982, 1984) carry out the biotransformation of geraniol (3) and nerol (7) by a totally different pathway. All these living systems specifically carry out the oxidation of the C-8 methyl (ω -methyl) group of acyclic monoterpene alcohols. This observation has prompted us to find a microbial system that has the ability to mimic the mode of metabolism of acyclic monoterpene alcohols observed in fungi, higher plants and mammals. A search for such a microbial system led to the isolation of a very versatile soil pseudomonad, identified as *Pseudomonas incognita*, capable of utilizing geraniol (3), nerol (7), citronellol (1), linalool (8), α -terpineol (9) and their corresponding acetates as the carbon source. Isolation of this versatile micro-organism has given us an opportunity to study the pathways of degradation of acyclic monoterpene alcohols and compare the chemical logic of microbial processes to that seen in the higher plant, fungal and mammalian systems.

2. Metabolism of linalool and linalyl acetate

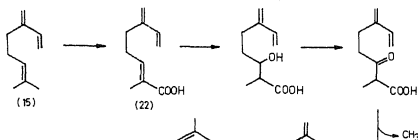
P. incognita was initially isolated on linalool (8) and hence it was of interest to establish its mode of metabolism in this organism. Isolation and identification of various metabolites from the culture medium have clearly indicated the existence of atleast two different pathways for the biodegradation of linalool (Madyastha *et al* 1977). One of the pathways (figure 2) appears to be initiated by the specific oxygenation of the C-8 methyl group of linalool (8) to 8-hydroxy linalool (10) which further undergoes step-wise oxidation in the presence of NAD-linked dehydrogenases to linalool-8-aldehyde and then to linalool-8-carboxylic acid (11). The second metabolic route consists of prototropic cyclization of linalool to α -terpineol (9) and its further degradation proceeds through the progressive oxidation of the C-10 methyl to yield oleuropeic acid (12). Besides, the presence of linalool oxide (13) and an unsaturated lactone (14) has been noticed. The formation of these compounds probably proceeds through the epoxidation of the 6,7-double bond which on further oxidation could give rise to these



compounds. Chemical analogies of such reactions have been reported earlier (Felix *et al* 1963).

The C-8 methyl oxidation of linalool by a *Pseudomonas* sp. has been reported earlier (Murakami *et al* 1973). In a similar way, the degradation of β -myrcene (15) by a strain of *Pseudomonas putida* (figure 3) commences with the oxidation of the C-8 methyl group (Narushima *et al* 1981). None of the metabolites isolated so far in the linalool fermentation suggests the possible oxidation of the C-1 position (figure 2). In the mammalian metabolism of β -myrcene, the terminal methylene groups are epoxidated and opening of the epoxides lead to the formation of diols (Madyastha and Vatsan, Unpublished observation). However, such a phenomenon is not observed in the microbial degradation of linalool. The interesting aspect of linalool metabolism by *P. incognita* is its ability to initiate one of the major energy-yielding pathways by the specific ω -methyl (C-8 methyl) oxygenation, whereas it fails to carry out similar oxidation with geraniol, nerol and citronellol, although these acyclic monoterpene alcohols are closely related to linalool. The mode of further metabolism of linalool-8-carboxylic acid (11) and oleuropeic acid (12) becomes reasonably clear from the degradation studies carried out with linalyl acetate (16).

P. incognita accepts linalyl acetate (16) better than linalool (8) as the sole source of carbon (Renganathan and Madyastha 1983). Hence it was of interest to find out whether the organism initiates the degradation of linalyl acetate by hydrolyzing the acetate to free alcohol or it has the ability to metabolize the molecule keeping the acetate moiety intact. cursory examination of various metabolites isolated from the culture medium indicates the existence of atleast three different pathways for the microbial degradation of linalyl acetate (figure 4, Renganathan and Madyastha 1983). Pathways A and C (figure 4) involve hydrolysis of linalyl acetate to linalool which gets further metabolized as discussed earlier (figure 2). The striking aspect of the third pathway (B, figure 4) is the unique ability of the organism to degrade linalyl acetate while keeping the acetate moiety intact as evidenced by the isolation of linalyl acetate-8-carboxylic acid (17) and Δ^5 -4-acetoxy-4-methyl hexenoic acid (18) from the culture medium. The formation of linalyl acetate-8-carboxylic acid proceeds in a manner similar to the formation of linalool-8-carboxylic acid (11) from linalool (figure 2). Further, it has been established that NAD-dependent alcohol and aldehyde dehydrogenases catalyze the conversion of 8-hydroxy linalyl acetate (19) to its corresponding acid. The linalyl acetate grown cells readily convert linalyl acetate-8-aldehyde to Δ^5 -4-acetoxy-4-methyl hexenoic acid (18) suggesting that the 6,7 double



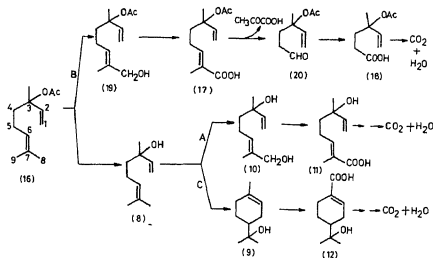


Figure 4. Probable pathways of degradation of linalyl acetate (16) by *P. incognita*.

bond cleavage occurs only after the oxidation of the C-8 methyl group. One of the possible modes for the cleavage of the 6,7 double bond is through epoxidation of the double bond and subsequent opening of the epoxide to the corresponding diol. The resulting diol may be cleaved in a manner similar to the periodate oxidation of diol to Δ^5 -4-acetoxy-4-methyl hexenal (20) and pyruvic acid. The hexenal (20) may be dehydrogenated to hexenoic acid (18). The other possibility of formation of hexenoic acid (18) is through the β -oxidation of linalyl acetate-8-carboxylic acid (17). In this mode of cleavage, one would expect Δ^5 -4-acetoxy-4-methyl hexenoic acid (18) and propionic acid as the products of degradation. Similar mode of cleavage has been postulated in the microbial degradation of β -myrcene (Narushima *et al* 1981, figure 3) where 4-methylenhex-5-enoic acid (21) is derived from 2-methyl-6-methylen-trans-oct-2,7-dienoic acid (22) through the β -keto oxidation pathway with the elimination of a propionic acid moiety. However, pyruvic acid has been shown to be formed when linalyl acetate-8-aldehyde is incubated with resting cells indicating that the former mode of double bond fission is operative.

The degradation of linalyl acetate (16) by *P. incognita* clearly indicates that part of it gets hydrolyzed to linalool. Several investigators have reported the asymmetric hydrolysis of ($\pm$) esters to optically active alcohols by micro-organisms (Fried *et al* 1971; Oritani and Yamashita 1974, 1980). In fact the high enantioselectivity of micro-organisms are often used in the synthesis of chiral organic compounds. Earlier it has been reported that *Bacillus subtilis var niger* hydrolyses racemic linalyl acetate to optically active linalool and acetate of its antipode (Oritani and Yamashita 1973). However, *P. incognita* fails to carry out the enantioselective hydrolysis of racemic linalyl acetate.

3. Metabolism of structurally modified acyclic monoterpenes

In order to ascertain the structural requirements of *P. incognita* to accept acyclic monoterpenes as substrates, its ability to degrade structurally modified linalool and linalyl acetate such as 1,2-dihydrolinalool (23), 1,2-dihydrolinalyl acetate (24), 2,6-

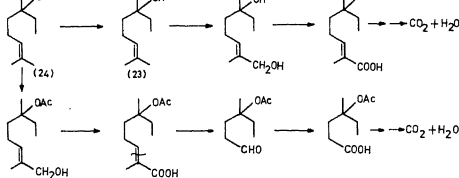


Figure 5. Probable pathways of degradation of 1,2-dihydrolinalyl acetate by *P. incognita*.

dimethyl octane have been studied. Although micro-organisms show great diversity in metabolizing a large number of chemicals, the number of degradative pathways are limited in nature. Often the presence of a single extra enzyme enables the organism to thrive on diverse substrates. However, it has been noticed in the case of 1,2-dihydrolinalool (23) and its corresponding acetate, that the organism fails to convert them to the nearest naturally occurring substrate, linalool and linalyl acetate, before they are further metabolized (Renganathan and Madyastha 1984). The mode of degradation of 1,2-dihydrolinalyl acetate is very similar to that observed for linalyl acetate (figure 5). The organism has shown its ability to grow on 2,6-dimethyl oct-2-ene and 2,6-dimethyl oct-2,6-diene whereas it fails to accept tetrahydrolinalyl acetate and 2,6-dimethyl octane. This observation clearly suggests that 6,7-double bond appears to be an essential structural requirement for these compounds to act as a substrate for this organism.

4. Metabolism of α -terpineol by *P. incognita*

As discussed earlier, one of the pathways for the degradation of linalool and linalyl acetate is initiated by the prototropic cyclization of linalool to α -terpineol (Madyastha *et al* 1977; Renganathan and Madyastha 1983). Besides, α -terpineol has been implicated as one of the intermediates in the microbial degradation of α - and β -pinenes (Shukla and Bhattacharyya 1968). However, earlier studies have failed to establish firmly the degradative pathways of α -terpineol (9). Hence studies were undertaken to get a better insight into the mode of metabolism of α -terpineol by *P. incognita*. On the basis of various metabolites isolated from the culture medium together with the supporting evidence obtained from enzymatic and growth studies, it appears that the organism degrades α -terpineol by atleast three different pathways (Renganathan and Madyastha, Unpublished observation). Among them, pathways A and B seem to be initiated by the oxygenation of the C-7 methyl group of α -terpineol/limonene resulting in the formation of oleuropyl alcohol/perillyl alcohol which further undergoes progressive oxidation to oleuropeic acid (12)/perillic acid (25). 1-Hydroxy-4-isopropenyl-cyclohexane-1-carboxylic acid (26) is presumably formed either from oleuropeic acid through elimination of the tertiary hydroxyl group as water and hydration of the 1,2 double bond or from limonene (27) through the intermediacy of perillic acid (figure 6). In fact limonene has been shown as one of the metabolites derived from α -terpineol (Renganathan and Madyastha, Unpublished observation). The pathways for the

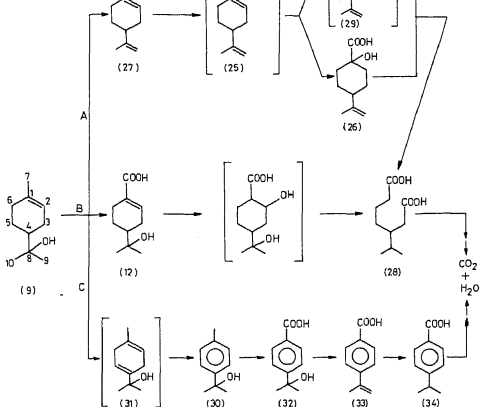


Figure 6. Probable pathways of degradation of α -terpineol (9) by *P. incognita*.

degradation of limonene by PL-strain have been established earlier (Dhavalikar and Bhattacharyya 1966). One can envisage the formation of β -isopropyl pimelic acid (28) either from 1-hydroxy-4-isopropenyl-cyclohexane-1-carboxylic acid (26) or from 2-hydroxy-4-isopropenyl-cyclohexane-1-carboxylic acid (29). The latter acid could arise from perillic acid (25) through the hydration of the 1,2-double bond. In both the cases, the ring fission is expected to proceed between C-1 and C-2 positions, followed by the reduction of the double bond to yield β -isopropyl pimelic acid (28). A similar mode of cleavage has been postulated earlier in the microbial systems (Shukla and Bhattacharyya 1968; Tsukamoto *et al* 1977).

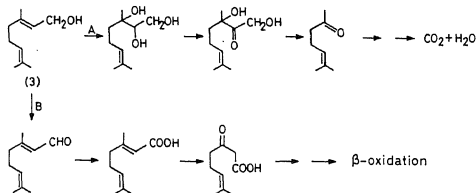
The third pathway (figure 6C) involved in the degradation of α -terpineol is the most interesting one. In this pathway, the organism aromatizes α -terpineol to p -cymene-8-ol (30) possibly *via* the intermediacy of cyclohexadiene(s). Aromatization of monoterpene by a microbial system has not been documented before, although such a process is believed to take place in higher plants (Poulouse and Croteau 1978). The co-occurrence of p -cymene-8-ol with structurally related cyclohexadienes such as γ -terpinene suggests their biogenetic relationship. The isolation of p -cymene-8-ol from the culture medium implies that α -terpineol undergoes desaturation possibly producing γ -terpinene-8-ol (31) which further gets aromatized to p -cymene-8-ol (30). The postulated intermediacy of γ -terpinene-8-ol (31) during the aromatization of α -terpineol is supported by the fact that the organism readily accepts α -terpinene, γ -terpinene and α -phellandrene as growth substrates. Subsequent to the formation of p -cymene-8-ol (30), the C-7 methyl

group undergoes progressive oxidation to 8-hydroxycumic acid (32). One could envisage the formation of 4-isopropenyl benzoic acid (33) from 8-hydroxycumic acid through the elimination of the tertiary hydroxyl group. Reduction of the double bond in 4-isopropenyl benzoic acid could give rise to cumic acid (34). The different enzymatic steps involved in the conversion of *p*-cymene-8-ol to cumic acid has also been established. It is quite possible that further metabolism of cumic acid may proceed as proposed earlier (Madyastha and Bhattacharyya 1968a, b; DeFrank and Ribbons 1977a, b).

5. Degradation of geraniol, nerol, citronellol and their corresponding acetates

P. incognita degrades the monoterpene alcohol, geraniol into a number of neutral and acidic metabolites (Rama Devi and Bhattacharyya 1977). Atleast two pathways for its degradation have been proposed (figure 7 A and B). Pathway A involves an oxidative attack of the 2,3-double bond resulting in the formation of an epoxide. Opening of the epoxide yields the triol which upon oxidation forms a ketodiol. The ketodiol is probably converted to 6-methyl-hept-5-en-2-one by a retro-aldol type reaction. Pathway B is initiated by the oxidation of the primary alcoholic group to geranic acid (4) and further metabolism follows the interesting mechanism proposed earlier (Seubert *et al* 1963; Seubert and Remberger 1963). The ability of *P. incognita* to degrade geraniol by atleast two distinct pathways proves its superiority over *P. citronellolis*. In the case of nerol (7) (the *cis*-isomer of geraniol) the degradative pathways analogous to pathways A and B as in geraniol are observed.

It has been observed that *P. incognita* metabolizes acetates of geraniol, nerol and citronellol much faster than their respective alcohols (Madyastha and Renganathan 1983). Blocking the primary alcoholic function by an acetate moiety has not changed the pattern of their degradation. However, the organism does not have the ability to metabolize these compounds keeping the acetate moiety intact as has been noticed in the case of linalyl acetate (Renganathan and Madyastha 1983) and 1,2-dihydrolinalyl acetate (Renganathan and Madyastha 1984). The metabolites isolated from geranyl acetate are geraniol (3), geranic acid (4) and 3-hydroxy citronellic acid (35), and from neryl acetate are nerol (7), neranic acid (6), 2,3-epoxide of nerol (36) and 3-hydroxy citronellic acid (35) (figure 8). The geranic or neranic acid formed possibly gets further metabolized as described earlier. 3-Hydroxy citronellic acid has not been shown to be



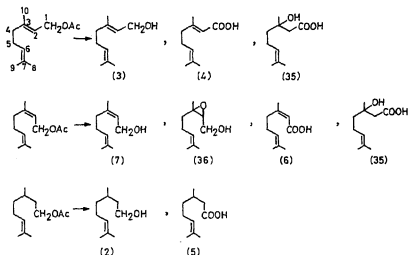


Figure 8. Metabolites of the acetates of geraniol, nerol and citronellol.

formed during the metabolism of geraniol and nerol by *P. citroneolliis* (Seubert *et al* 1963). This acid could have been formed by the hydration of the 2,3-double bond of geranic and neranic acid. The significance of this compound in the overall metabolism is not known. It is quite possible that one of the pathways for the degradation of geranyl acetate and neryl acetate converge at 3-hydroxy citronellic acid (35) and from thereon a single pathway may operate for their further metabolism. However, the mode of further degradation of 3-hydroxy citronellic acid has not been established. In contrast to the earlier findings (Seubert and Fass 1964), it appears that *P. incognita* metabolizes geraniol through geranic acid without isomerizing to neranic acid (Madyastha and Renganathan 1983). This has been established by the GC and NMR studies of the methyl esters of the acidic metabolites derived from geranyl acetate.

There has been only limited work carried out so far on the fungal transformations of monoterpenes. Most of these pertain to the transformations of terpene hydrocarbons by fungal system (Prema and Bhattacharyya 1962). Since monoterpene alcohols have considerable antifungal activity, their transformations have not been studied so far. However, a strain of *Aspergillus niger* has been isolated in our laboratory which has the unique ability to transform geraniol, citronellol and linalool to their respective 8-hydroxylated derivatives (Madyastha and Murthi, Unpublished observation). Since free alcohols are toxic to the organism, corresponding acetates have been used in this study.

Examination of the various metabolic pathways of different acyclic monoterpenes by *P. incognita*, reveals that in certain respects, these degradative pathways are similar to their bio-transformation in fungi, higher plants and mammalian systems. One of the striking similarities of all these living systems is their ability to carry out specific ω -methyl hydroxylation of some of the acyclic monoterpene alcohols. It is interesting to note that the higher plant, bacterial and mammalian ω -hydroxylation reaction is mediated by a cytochrome P-450 system. Cytochrome P-450, a haemoprotein, which has the ability to generate a highly reactive hydroxylating species from molecular oxygen. The hydroxylating species is generated from the Fe(II) state of the cytochrome, which is formed by reduction of the Fe(III) oxidation state.

The biochemical pathways involved for the degradation of geraniol, nerol and

dihydrolinalool and their corresponding acetates. Unlike linalool, the prototropic cyclization of geraniol and nerol has not been observed in *P. incognita*, although conformationally nerol and linalool are very close to each other. Perhaps the logic behind the prototropic rearrangement of linalool to α -terpineol is to converge the catabolic sequence to a specific intermediate which is common for number of structurally related compounds. This is exemplified in the metabolism of α - and β -pinenes by the PL-strain where the rupture of the cyclobutane ring of pinene results in the formation of a *p*-menthenoid cation which can be neutralized through the loss of a proton or by the attack of a hydride or hydroxide ion to yield limonene, *p*-menth-1-ene and α -terpineol (Shukla and Bhattacharyya 1968).

Although micro-organisms have great ability to metabolize a large variety of compounds, the number of biochemical pathways are limited in nature. It is against the cell economy for a microbe with diverse metabolic capacities to have unique degradative pathways for different compounds. Normally microbes have the ability to converge the catabolic sequence of different compounds to a limited number of intermediates and thereon a common pathway operates thus indicating the genetic economy that exists in micro-organisms.

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Evolution of the genetic code: Chemical studies on the genesis of coded α -amino acids

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Abstract. The choice of the twenty coded L- α -amino acids from innumerable such possibilities has been correlated to selection based on structural versatility and the ability to accommodate new entrants as a function of time. This, in turn, favours an evolutionary profile for the genetic code, an idea that finds much support on the basis of a close examination of the pattern of degeneracy that is present. The focus of the experiments reported in the present paper is to delineate pathways that would lead to a centrally controlled synthesis of α -amino acids and to the selective replacement of one amino acid with another in intact peptides. These endeavours would also be appropriate in the context of the current demonstration that the replacement of a single amino acid residue with another could bring about profound biological changes.

N-trityl serine methyl ester-O-mesylate and N-benzoyl serine methyl ester-O-mesylate have been demonstrated as alanyl transfer synthons. The latter synthon is quite effective and it has been already transformed to N-benzoyl phenylalanine methyl ester, N-benzoyl leucine methyl ester and N-benzoyl tryptophan methyl ester via reaction with appropriate organo cuprate reagents. In principle, as many as 14 of the twenty coded amino acids could be derived in a similar manner from this synthon.

N-benzoyl phenyl alanine methyl ester (BzN-Phe-OMe), BzN-Phe-Phe-OMe and BzN-Phe-Phe-Phe-OMe have been transformed to, respectively, Bz-Asp-OMe, Bz-Asp-Asp-OMe and BzN-Asp-Asp-Asp-OMe in good yields via controlled oxidation with RuO_4 in aqueous acetonitrile. Benzoyl aspartic acid cyclohexyl amide- β -methyl ester has been transformed to NBz-Leu-OMe via Grignard addition and selective dehydroxylation. Thus, the methodology for the Phe $\rightarrow$ Leu change, of importance with respect to evolution of code, has been delineated.

Whilst the structural relationship between phenyl alanine and leucine is obvious, that in the case of the pair histidine-glutamine is not. Glutamine precursors have been obtained in a single step *via* oxidation of Bz-His-OMe with RuO_4 . The mechanism of formation of the products has been delineated by model studies. A formamidomethyl transfer synthon, of potential use in the Gln $\rightarrow$ His change, has been prepared, and a cycloaddition strategy for the transformation is described.

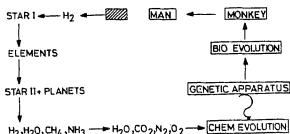
Keywords. Coded α -amino acids; centrally controlled synthesis; side-chain interconversions.

The realisation that Nature obeys the laws of chemistry has led to endeavours relating to the understanding, on a molecular basis, the origin of life itself. A system can be said to be alive if it can sustain and replicate with the assistance of its inbred memory and mechanisms. In chart I, a rational interpretation leading to the evolution of life in our planet is presented.

Whilst processes including the chemical evolution on the one hand and those related to the Darwinian evolution on the other, can be comprehended on a rational basis, the transformation of molecules of diverse complexity to a self-replicating proto-cell is an area that remains to be understood. The overall metamorphosis associated with the organization of molecules to a proto-cell is a consequence of the operation of

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CHART I



innumerable molecular changes and it is currently generally accepted (Kuhn 1972; Kuhn *et al* 1981) that the best way to understand the formation of a self-replicating proto-cell is to cogently explain the most crucial, if not all, the events that must be related to the formation of life on a molecular basis and in terms of the accepted pathways for molecular transformations.

The present paper endeavours to synthesize, using theory, inference and experiments, an approach to the understanding of the genesis of the coded amino acids, which, in turn, linked through the genetic code, could lead to an important contribution pertaining to the genesis of the information system, which is a prerequisite for life. This is a domain that has hitherto been rarely dwelled upon. Indeed, even basic questions such as the logic of selection and sustenance over millennia, of 20 (L) α -amino acids, from a pool of several hundred thousand possibilities of which about 400 are found in nature and the non-randomness of the code await rational explanation. There is no doubt that the choice of these 20 amino acids must be a result of evolution over long periods, which would imply that the genetic code must have inherent in it, facets that would be a pointer to the evolution of the genetic code itself. Consequently, there is a crucial relationship between the structures of the coded amino acids, that vary only as a function of side chain, and the 64 triplets that constitutes the genetic code.

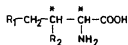
Time has obliterated direct evidence relating to the evolution of the code, if such were the case. Amongst the lines that may be pursued to secure indirect evidence pertaining to this, could be the understanding of logic behind the amino acid changes that are associated with essential protein families such as cytochromes, haemoglobins, or hormones such as insulin, oxytocin, vasopressin, as a function of evolution across a large time span. Another possible approach to this problem could be the synthesis of peptides, which might be an ancient precursor to those that exist today based on the probability that amino acid introduction was a progressive feature and accommodated by lifting the degeneracy of the genetic code. Both these approaches take cognizance of the choice of the 20 L- α -amino acids in our information system, from amongst the many possibilities available. From a totally synthetic point of view, an advantageous approach to such a choice would be to generate these from as few precursors or synthons as possible. Indeed, in nature also, more than half the complement of the α -amino acids arise from side chain transformation of serine and aspartic acid. Besides, the 20 α -amino acids could be arranged into two major structural types as illustrated in chart II and chart III.

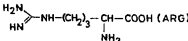
Ten of the 20 coded amino acids could be considered as derivatives of alanine, that is, they could, in principle, be generated from the common grouping, namely, the alanyl synthon and therefore structurally represented as R-ala. Both from biosynthetic and

CHART II

R-CH ₂ -CH(NH ₂)-COOH							
No.	R	NAME	NATURE	No.	R	NAME	NATURE
1	-H	ALA	H	5	-OH	SER	P
2	-CH(CH ₃) ₂	LEU	H	6	-SH	CYS	P
3		PHE	H	7		TYR	P
4		TRP	H	8		HIS	P
				9	-CONH ₂	ASN	P
				10	-COOH	ASP	A

CHART III



No.	R ₁	R ₂	NAME	NATURE	No.	R ₁	R ₂	NAME	NATURE
11.	-SCH ₃	-H	MET	P	14.	-H	-CH ₃	VAL	H
12.	-CONH ₂	-H	GLN	P	15.	-H	-CH ₂ CH ₃	ILE	H
13.	-COOH	-H	GLU	A	16.	-H	-OH	THR	P
17.	H ₂ N-CH ₂ -COOH (GLY)								
18.	H ₂ N-(CH ₂) ₄ -CH(NH ₂)-COOH (LYS)								
19.									
20.									

present in serine (R=OH), cysteine (R=SH), aspartic acid (R=COOH) and asparagine (R=CONH₂). In the present work, aspects of this have been successfully simulated synthetically. As mentioned previously, biosynthetically also, most coded amino acids arise from precursors cited above. In chart III are shown a set of six amino acids, three of which, namely, methionine, glutamine and glutamic acid could be considered as derived from the homoalanyl synthon and the remaining three as β -substituted homoalanines. Thus, sixteen of the twenty coded amino acids can be correlated to common precursors. Of the remaining four (chart III), glycine is a unique one, being the simplest and the only one having no chiral centre. The basic amino acids lysine and arginine have their functional groups well separated from the peptide backbone to minimize rupture of the protein backbone by intramolecular protonation. The remaining coded amino acid, namely, proline is the only one that defies classification.

All rationalizations, at the molecular level, relating to the formation of the proto cell from precursors, are in agreement with the development of the information system or the genetic code as a result of increasingly sophisticated mechanisms involving nucleic acid-nucleic acid interactions on one hand and nucleic acid-protein on the other. This would imply a relatively late origin for the triplet code. Consequently, the experimental establishment for an evolutionary nature of the code will provide support for theory, viewed from diverse perspectives. It is almost certain that the code initially referred to fewer than the 20 amino acids, for which it stands today. Two questions logically arise, namely, the nature of the primitive code and the description of the primitive amino acids. With reference to the code, another logical criteria has to be annexed, that is, any change of its profile should not disrupt evolutionary processes already in vogue (Crick 1968). A simple solution to this would be an assignment of total degeneracy to the code with reference to the last letter. In sum, it would imply a doublet code. This is reasonable, since, even in the present day translation machinery, 7 out of the 20 amino acids have a "de-facto" doublet code. According to this rationalization, in its early history, all the codes were doublets and, as a function of evolution, late amino acids that imparted advantages were incorporated by lifting of the degeneracy of the code. With reference to the nature of the amino acids that were coded from the beginning, the doublet code could have recognised perhaps as few as eight α -amino acids and these too

molecular structure (Woese 1967). Parenthetically, the 20 α -amino acids currently in vogue could be classified into four categories, namely, hydrophobic, polar, largely basic and largely acidic. A striking feature of the code is that the triplets related to each four categories are bunched together, an aspect that would be in harmony with an initial selection that was not necessarily based on exact molecular structure. The implication of this is that, enzyme activity which plays a central role, had a modest or even fortuitous origin and that the enzyme systems are connected with imparting the needed tilt in favour of assertive organisations. The genetic code is presented in table 1.

The genetic code should hold key facets that are relevant to the very origins of life. This is best reflected in the fact that although degeneracy is anticipated since 64 triplets stand for 20 α -amino acids, this degeneracy is not uniform. Chart IV illustrates this aspect of the genetic code.

We have, in chart IV, re-arranged the genetic code into five groups. Type A refer to seven amino-acids, which have a "de-facto" doublet code even today, in the sense that the third letter is totally degenerate. Of great significance are the ten amino acids presented as five pairs in category B, wherein each pair has a common doublet as well as the consistent use of, as the third letter, pyrimidines (U, C) to denote one partner and

Table 1. Genetic Code for amino acids.

First position (5' end)	Second position				Third position (3' end)
	U	C	A	G	
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Term	Term	A
	Leu	Ser	Term	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

CHART IV

A	B	D
LEU (CU)	PHE-LEU (UU/U, C-A, G)	ILE (AU/U, C, A)
VAL (GU)	SER-ARG (AG/U, C-A, G)	MET (AUG)
SER (UC)	ASN-LYS (AA/U, C-A, G)	<u>E</u>
PRO (CC)	HIS-GLN (CA/U, C-A, G)	CYS (UG/U, C)
THR (AC)	ASP-GLU (GA/U, C-A, G)	TERM (UGA)
ALA (CG)	G	TRP (UGG)

opinion, that these pairs are historically related and that the degeneracy pertaining to the third letter was partially lifted to accommodate a more recent and in many cases a structurally similar amino acid. For example, it could be envisaged that in certain situations, leucine residues in early proteins, were, as a function of evolution, replaced by phenylalanine. Most pairs in category-B, could be historically so related. This notion is amenable to experimental scrutiny, provided suitable methods can be developed to replace one of the partners with the other in intact proteins. Such an approach would, in addition, lead to strategies for the restructuring of the protein *via* side chain metamorphosis, thus reducing synthetic arduours of classical procedures. In type C, we have tyrosine-termination codon pair much as in the situation in category B. In this case, it is possible that the degeneracy pertaining to termination codon was lifted partially to accommodate the late arrival tyrosine. Perhaps, a converse of this is illustrated in type D, where isoleucine degeneracy is partially lifted to accommodate the initiator codon methionine. Again, a similar situation can be observed in type E, where the cysteine has taken up the pyrimidine pair and the purines shared between a terminal codon and tryptophan, perhaps the most complex of the coded α -amino acids. Tryptophan, is most definitely a candidate for late inclusion and this could explain the unique triplet code assigned to it.

Common functional proteins and hormones are present in living systems that are separated by a very large time gap. Amino acid analysis of these compounds (Eck *et al* 1966) has demonstrated replacement of some amino acid residues with others. Barring few exceptions, it has so far been not possible to design a common logical pattern for such replacements, with reference to the needs of the particular living species. However, it would be too unrealistic to conclude that these replacements are a result of only random mutations.

A key feature of the evolutionary model presented here for the genetic code is the notion that incorporation of late amino acids is accommodated by lifting of the degeneracy that is present. As pointed out earlier, since, by and large, amino acids of the same type are bunched together in the code, this incorporation would amount to the adaption of the α -amino acids of the same characteristics. That this alteration is of profound significance is best illustrated with the relatively simple molecules that constitute the neurohypophyseal hormones which are produced in the pituitary and which are present in species separated in the evolutionary scale, by as much as three hundred million years. In each of these species two hormones are present which have a common structural pattern characterised by nine amino acid residues with a disulphide bridge connecting the amino acids in position 1 and 6 (chart V).

Isotocin, mesotocin and oxytocin exert control in reproduction, and vasotocin, vasopressin in the regulation of salt and water balance. It may be noted, that the transformation of vasotocin which is present in amphibians to vasopressin that is present in land animals, requires only the substitution of phenyl-alanine for isoleucine in position 3 (chart V). Although, chemically this is merely an interchange between two hydrophobic groups, it precipitates great biological changes which are required to maintain a vastly different ion water retention pattern required in land animals (Acher 1966; Woese 1967). Thus, whereas vasotocin promotes water secretion, vasopressin conserves retention of water. It must be admitted, that this is one of the rare cases where the replacement of a single amino acid residue can be well correlated with evolution. However it is likely that in several cases, there may be present, valid reasons for the

CHART V

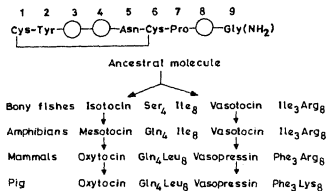
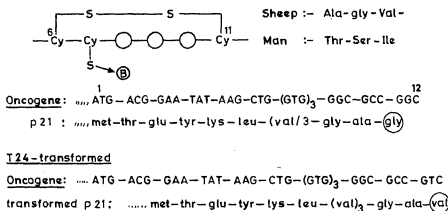
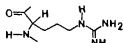


CHART VI

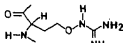


choice of particular amino acid. Less direct proof for the relationship between pairs of amino acids cited in chart IV(B) is also available from comparison of the amino acid sequences of cytochromes of several species separated by a long time span in evolution which show that in several cases leucine has been replaced by phenylalanine, lysine with asparagine and glutamic acid with aspartic acid (Woese 1967). Parenthetically, there appears to be a special relationship between lysine and asparagine. The protein sequence of haemoglobin from patients suffering from hereditary disorders demonstrates that in several cases lysine and asparagine are interchanged. The replacement of as little as one amino acid residue in a protein containing as many as hundred amino acids could have profound biological implications. This has been most dramatically illustrated from studies on the mechanism of the transformation of a harmless oncogene in humans to one that is malignant. Painstaking experimentation pertaining to this transformation by two independent groups has shown that protein p 21 arising from the oncogene on being made infectious by T 24 causes a single mutation in the appropriate genome, transforming the triplet GGC to GTC, which, on translation, would involve the replacement of a glycine residue with valine! Thus, the transformed malignant protein p 21 differs from normal one by one amino acid! Further experiments have shown that even this apparently minor change causes marked differences in the electrophoretic behaviour of the two proteins (chart VI) (Tabin *et al* 1982; Reddy *et al* 1982).

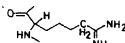
CHART VII



ARGININE



CANAVANINE



INDOSPICINE

biological, biochemical and toxicological properties. Many toxic situations arise, leading to severe biological malfunctioning, as a result of incorporation of such amino acids in the place of the coded ones by cells that are unable to distinguish the structural difference. Such differences can indeed be very minor and this aspect can best be demonstrated by comparison of the coded amino acid arginine with the toxic non-coded amino acids, canavanine and indospicine (chart VII).

The first book on this subject, which has recently appeared, gives an account of the profound changes that may take place by even a minor error in the choice of appropriate amino acids (Rosenthal 1982).

The long range objectives of our work in this area, the preliminary results of which are presented here, are,

- (i) to develop practical methods, using the tools available to the organic chemist, for the preparation of as many coded α -amino acids as possible from a common precursor.
- (ii) the selective transformation of one amino acid residue to another in intact peptides with focus in the first phase on the transformation of α -amino acid pairs cited under category B (chart IV). It could be readily seen that the experiments planned under (i) would be also related to the objectives under (ii).

It is hoped that these objectives would be of relevance not only with respect to the problem at hand but also could provide an alternate method for protein synthesis as well as to capabilities for chemically effecting unit replacements. A useful outcome of such an accomplishment would be the ability to replace, as can be done enzymatically presently, the five amino acid residues from sheep insulin with the corresponding unit of human insulin as illustrated in chart VI.

The preparation of an alanyl transfer synthon, a precursor to chiral alanine derived α -amino acids:

The strategy that was adopted for the preparation of an alanyl transfer synthon is shown in chart VIII.

It was anticipated that the readily available α -amino acid, serine can be transformed to an alanyl unit possessing a desired leaving group, which, in turn, could be replaced by an appropriate "R" moiety. The alanyl synthon thus conceived could belong to the several types as shown in chart VIII.

N-trityl serine methyl ester-O-mesylate was prepared from L-serine. In preliminary experiments, when this synthon was reacted with nucleophiles having an alkali metal counter ion, the major product isolated was the dehydro-amino acid, which, in principle, could serve as an achiral alanyl synthon. Interestingly, it was found that the reaction of mesylate with NaI/Zn in DME gave in excellent yields, the chiral cyclic amino acid ester (chart IX). Subsequently, it was possible to make quantities of this N-protected aziridine ester directly from serine methyl ester hydrochloride in a one flask reaction (Smrt *et al* 1957) (chart X).

CHART VIII

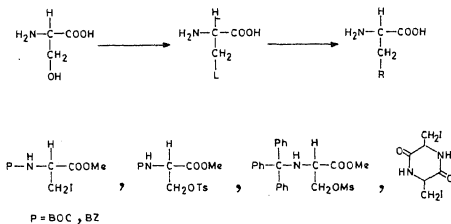


CHART IX

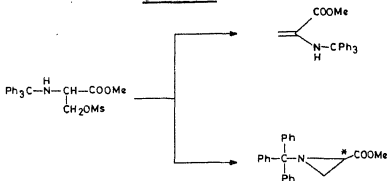
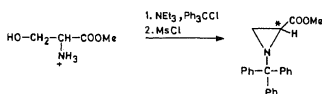


CHART X



The ready availability of the chiral N-trityl aziridine, suggested it to be an attractive synthon for the generation of the alanyl residue *via* nucleophilic attack at the unsubstituted methylene carbon. Accordingly, the aziridinium ion (chart XI) was prepared at -70° by addition of exactly one equivalent of ethereal HCl. In the event, every attempt to open the aziridinium system (Deyrup, 1982) led to the isolation of only the chloride opened products, thus indicating the propensity for the internal return rather than external nucleophilic displacement (chart XI).

In control experiments (chart XI), the aziridine system was treated with one equivalent of ethereal HCl at -70° and allowed to warm up to room temperature. When chloroform was used as a solvent, the product was the expected N-trityl- β -chloroalanine methyl ester. In sharp contrast in DME the β alanine product was formed. Finally, the aziridine, when treated with excess of ethereal HCl, underwent deprotection and ring opening giving rise to β chloro alanine methyl ester HCl (chart XI).

CHART XI

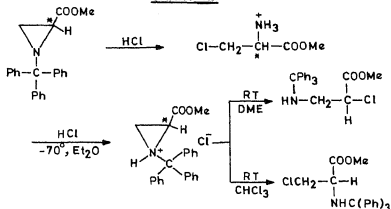
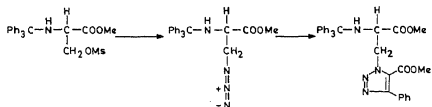


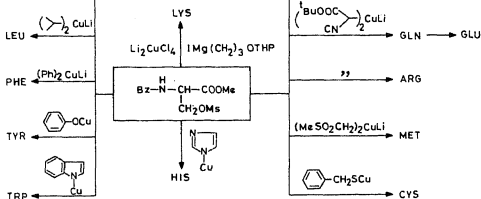
CHART XII



esters having an appropriate leaving group as the alanyl synthon. In preliminary experiments, the feasibility of this was established by reaction of N-trityl-Ser-OMe mesylate with azide ion followed by cycloaddition with methyl phenyl propiolate leading to a novel triazolyl alanine system (chart XII).

In subsequent experiments, it was found that a portion of the N-tritylated substrates underwent deprotection under conditions of the reactions thereby leading to reduced yields. Other protecting groups which were tried without success included the N-Benzyl as well as the N-t-butyl sulphenyl. Similarly, substrates with the nitrogen function protected *via* a carbonyl linkage were also not suitable for this reaction. The best synthon so far studied that could transfer the chiral alanine residue, is the N-Benzoyl serine methyl ester, having the leaving group either as tosylate or mesylate. Nucleophiles, having alkali metal counter ions were not suitable, since they brought about a great deal of elimination. We report, that the alanyl transfer synthon N-Benzoyl serine methyl ester-O-mesylate, could be effectively used in the synthesis of coded α -amino acids *via* reaction with appropriate organo-copper reagents. Thus, reaction of the alanyl synthon with freshly prepared diphenyl lithium cuprate at -70° gave N-benzoyl phenyl-alanine methyl ester in good yield (chart XIII).

The structural assignment for the product is based on spectral comparison with an authentic sample. Similarly, treatment of the alanyl synthon with *in situ* generated diisopropyl copper lithium and indolyl copper led to the formation of, respectively N-benzoyl leucine methyl ester and N-benzoyl tryptophan methyl ester. Thus, the usefulness of N-benzoyl serine methyl ester-O-mesylate as an alanyl transfer synthon has been clearly established. The capabilities of this synthon are illustrated in chart XIII, where it could be further used for the preparation of as many as fourteen of the twenty amino acids! We plan to explore further the full potential of this synthon and try



out that methodologies developed in this direction would enable the transformation of, at will, a serine residue in peptides to nearly most of the coded amino acids, thus affording a powerful tool in the synthesis of peptides.

Selective α -amino acid $\rightarrow$ α -amino acid metamorphosis in intact peptides:

In this section we describe our endeavours pertaining to the transformation of amino acids to the corresponding partner with which it shares a doublet (chart IV) (vide supra). The most appealing amongst these, is the transformation of phenyl alanine to leucine, which would, in sum, amount to the metamorphosis of a phenyl residue to an isopropyl one. Molecular models show that the structural changes associated with the replacement of a phenyl residue in a peptide with leucine would be marginal. Therefore it would be of great interest to study the properties of representative peptides, where a phenylalanine residue has been replaced by leucine, with reference to the possibility that the latter could have been a precursor to the former. In the case of small peptides that serve as hormones, the receptor site adaptability is of consequence and therefore a study of such modified hormones would enable, in addition, an assessment of the receptor site changes, as a function of evolution. From a synthetic point of view, there are only few methods available for the transformation of an aromatic residue with an aliphatic successor. All of these take advantage of the limited nucleophilic activity of the aromatic residue in terms of its reaction with oxidizing reagents. The task at hand then involved the transformation of the benzene ring of phenylalanine residue to an isopropyl one, not only with respect to the individual amino acid but also in intact peptides (chart XIV).

Of the several procedures that were attempted to oxidize the phenyl ring, the most promising turned out to be ruthenium tetroxide in aqueous acetonitrile (Sharpless *et al* 1981). Thus, it was possible to transform N-benzoyl phenylalanine methyl ester to N-benzoyl aspartic acid- α -methyl ester in excellent yields and with complete chiral retention. Parenthetically, as stated earlier, the side chain residue of aspartic acid and serine are good precursors for amino acid replacement in peptides. Therefore, the transformation of the phenyl residue in phenylalanine to the carboxyl function is of additional importance. We have subsequently demonstrated convincingly that this oxidation is feasible in intact peptides by transformation of both Bz-Phe-Phe-OMe and Bz-Phe-Phe-Phe-OMe to, respectively, Bz-Asp-Asp-OMe and Bz-Asp-Asp-Asp-

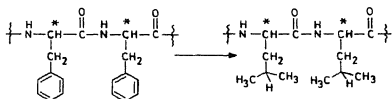


CHART XV

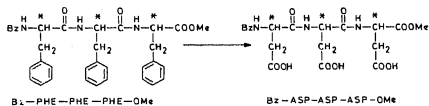
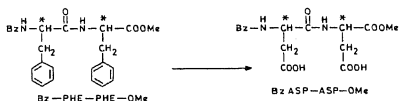
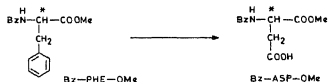
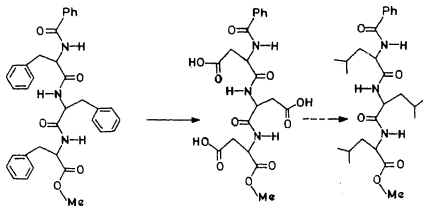


CHART XVI



OMe in good yields and chiral purity (chart XV). In chart XVI the Bz-Phe-Phe-Phe-OMe → Bz-Asp-Asp-Asp-OMe change is shown with focus on the peptide backbone.

The second stage in the Phe-Phe-Phe → Leu-Leu-Leu change (chart XVI) envisages the transformation of the carboxyl function to an isopropyl grouping. This aspect has

been demonstrated with the transformation of N-benzoyl aspartic acid cyclohexylamide- β -methyl ester, wherein the side chain, namely, $-\text{CH}_2\text{COOCH}_3$ function, is in an environment similar to that in peptides, to N-benzoyl-leucine-cyclohexylamide, *via* sequence, methyl Grignard addition to the tertiary alcohol and dehydroxylation with trimethyl silyl chloride and Zn/acetic acid (chart XVII).

Thus, it is now possible to transform a phenylalanine side chain in peptides to a leucine residue, provided there are no interfering residues. Work is in progress relating to the Phe $\rightarrow$ Leu change, by the procedures described here, in selected, biologically active peptides and to assess the potency of such modified proteins.

Whilst the structural similarity between phenylalanine and leucine is obvious, that between histidine and glutamine—another pair of amino acids that belong to category B chart IV—is latent. A common feature can however be discerned in the sense that the polar terminal nitrogen is situated in both these amino acids from the peptide backbone at the same distance. Additionally, it could be conceived that histidine may arise by reaction of glutamine, in a regio selective manner, with formamide or its equivalent. Amongst all the 20 coded α -amino acids, histidine plays the most crucial role in the sense that its presence has been identified at the active sites of enzymes more than any other amino acid. In view of this, it was considered to charter practical routes for the transformation of histidine (Code-CAU, CAC) to glutamine (Code-CAA, CAG) on the one hand and the reverse operation on the other. At the outset, it was considered expedient to transplant our experience pertaining to the oxidation of the aromatic ring in phenylalanine to aspartic acid, to the imidazole ring present in histidine. In the event, reaction of histidine with ruthenium tetroxide in acetonitrile was quite complex and the highly functionalized, crystalline carboxylic acid obtained in low yields from these experiments has been assigned, on mechanistic grounds (*vide infra*), a pyrrole structure (chart XIX). Reaction of N-benzoyl histidine methyl ester gave encouraging results. Reaction of this protected histidine with ruthenium tetroxide at pH 6 in aqueous acetonitrile gave two crystalline compounds, the first of which has been identified as N-

CHART XVII

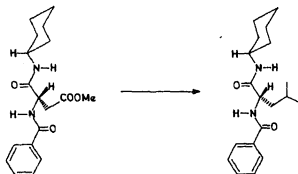


CHART XVIII



XIX). The second crystalline product was neutral and could be obtained consistently in about 30% yields. Based on spectral and analytical data and studies with model system, this compound is assigned the imidazolidine dione structure, shown in chart XIX.

This structure is of interest not only because it is very closely related to glutamine, to which it can be transformed, in principle, by rupture of the ring -CH-NH bond followed by hydrolysis, but also because it represents an intermediate stage in the transformation of glutamine to histidine, *via* incorporation of elements of formamide. It may be noted that the acidic product obtained could, by classical methods, be homologated readily to N-benzoyl-glutamine methyl ester. In order to understand the course of reaction of ruthenium tetroxide on histidine, the reaction was studied on the model system, tetrahydrobenzimidazole, prepared from α -chloro-cyclohexanone. This reaction gave as the sole product the interesting bicyclic system shown in chart XX.

We rationalized the formation of this by primary interaction of the reagent with the 2-position of the imidazole (Wasserman *et al* 1981), leading to a novel electrophilic and unstable 2,5-diazacyclopentadienone system which readily accepts elements of water giving rise to observed product. A similar mechanistic sequence would readily explain the products arising from the reaction of N-benzoyl-histidine methyl ester with ruthenium tetroxide as shown in chart XXI.

A similar series of events, as shown in chart XXII, would explain the formation of the highly polar carboxylic acid obtained when unsubstituted histidine was reacted with ruthenium tetroxide. It may be noted from chart XXII, that in this case, the key

CHART XIX

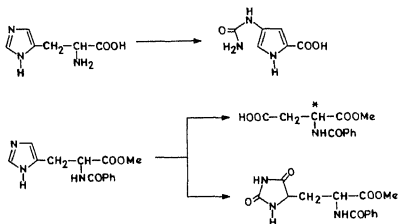
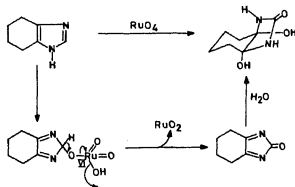


CHART XX



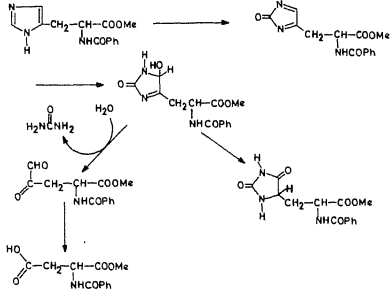
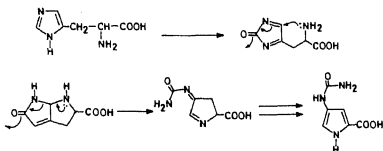


CHART XXII



electrophilic diazacyclopentadienone undergoes intramolecular Micheal type addition with the free amino group and the resulting bicyclic system readily reorganises to the aromatic pyrrole nucleus, the entire experience amounting to the liberation of the imidazole nitrogens from ring system, to be replaced by the pyrrole nucleus involving the cyclization of the α -amino acid residue. Pathways are currently under study for an effective method for the transformation of the imidazolidine dione (chart XIX) to glutamine.

The perception that an amide system could lead to imidazole *via* incorporation of elements of formamide led us to explore the possibility of the preparation of an appropriate synthon from formamide that could react with either an amide function or its equivalent leading to imidazole. Reaction of formamide with formalin and dimethylamine followed by methylation of the resulting Mannich product, gave, in good yields, the crystalline formamidomethyltrimethyl ammonium iodide, which has been demonstrated to be an excellent formidomethyl transfer synthon, on reaction with appropriate nucleophiles. Such formamido compounds have been transformed with triphenyl phosphine- CCl_4 to isocyanides and their conjugate bases have been shown to form imidazoles *via* cycloaddition with substituted nitrile functions (chart XXIII) (Van Heusen *et al* 1976).

Finally, asparagine has been converted to N-benzyl oxycarbonyl β -cyanoalanine methyl ester and endeavours are under way to transform this to N-benzylloxycarbonyl

CHART XXIII

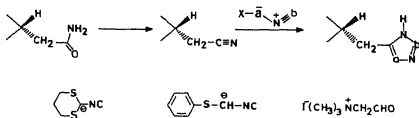
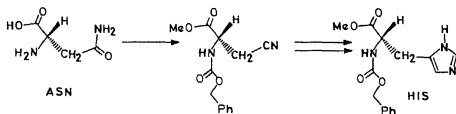


CHART XXIV



histidine methyl ester *via* cycloaddition with synthons described in chart XXIII (chart XXIV).

The results from investigations reported here, provide sufficient incentive to proceed further to reach the objectives outlined in the earlier part of the paper. Further, they are likely to lead to the addition of novel facets to synthetic methodologies.

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Peptides as bioorganic models

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Abstract. This article develops the possibility of using conformationally rigid peptides as bioorganic model systems. Stereochemical constraints on peptide backbone folding may be introduced by the judicious use of sequences containing α -aminoisobutyric acid and proline. The design of synthetic peptide models of 3_{10} -helical and β -turn conformations is reviewed. Attempts at generating model antiparallel β -sheet peptides are discussed. The use of disulphide crosslinks is illustrated in the application of cystine peptides to generate models for β -turn and antiparallel β -sheet conformations. Using a conformationally well-defined backbone as a skeleton attempts to generate models for protein binding sites are examined. Helical retinylidene-lysine peptides are introduced as models for the bacteriorhodopsin chromophore. Lysine containing peptides and chiral diamines are explored as model-binding sites for bilirubin and gossypol. An attempt to model the active site disulphide loop of the redox protein, thioredoxin, is described.

Keywords. Peptide conformation; bioorganic models; α -aminoisobutyryl peptides; bacteriorhodopsin; bilirubin; gossypol; thioredoxin; peptide models.

1. Introduction

Biological recognition processes involve extremely specific interactions between relatively complex molecules. Peptides and proteins often participate in important molecular recognition events in biology of which, receptor-effector, antigen-antibody and enzyme substrate interactions are a few well-known examples. The precise folding patterns of peptide backbones can serve to precisely orient functional sidechains in three-dimensional space. Proteins thus have the ability to generate remarkable molecular cavities, which provide a means of recognizing complementary structures. Studies in the area of biomimetic chemistry have resulted in the design of a variety of extraordinary structures which in turn have allowed the development of a wide range of 'host-guest' chemistry (Kellog 1982). Crown ethers, macrobicyclic cryptands, cyclophanes and cyclodextrins (Cram and Trueblood 1981; Weber and Vögtle 1981; Cram 1983; Breslow 1982; Lehn 1978; Cram and Katz 1983) provide illustrative examples of molecular surfaces, with specific binding abilities. The structural flexibility of peptide backbones and the multiplicity of sidechain conformations have severely limited attempts to design peptide structures, which will mimic the binding and functional characteristics of natural protein systems (Chakravarty *et al* 1973; Gutte *et al* 1979; Fukushima *et al* 1979; Schultz *et al* 1982; Moser *et al* 1983). It is clear that an understanding of the factors determining peptide chain folding must precede any attempt to rationally design and engineer the construction of a synthetic peptide with specific functional abilities. This article describes studies being carried out in the author's laboratory, which attempt to develop synthetic peptides as bioorganic model systems. Our interest in this area is based on studies of stereochemically constrained peptides, carried out during work aimed at understanding the conformation and

function of alamethicin and related membrane channel forming polypeptides (Nagaraj and Balaram 1981a; Mathew and Balaram 1983; Prasad and Balaram 1984). These systems contain high proportions of the unusual α,α -dialkylated amino acid, α -aminoisobutyric acid (Aib). The imino acids proline (Pro) and hydroxyproline (Hyp) also occur in these natural products. While examining the structural chemistry of peptides containing these residues it became clear that the stabilization of specific backbone conformations can be achieved using a judicious choice of sequences with Aib and Pro residues. Further restrictions on chain folding can be imposed by cyclization involving disulphide bridging between cysteine (Cys) residues in a given sequence. In this report a brief account of the design of peptides with defined backbone conformations is first presented, followed by a survey of a few examples of the use of peptides as model systems in bioorganic chemistry.

2. Design of conformationally defined peptides

2.1 Helical conformations

The peptide backbone has two main degrees of freedom about the N-C α (ϕ) and C α -CO(ψ) bonds, with the peptide units being largely restricted to a *trans* geometry ($\omega \sim 180^\circ$). For residues having only a single C α substituent, relatively large regions of ϕ , ψ space are stereochemically allowed and these are generally delineated on a two-dimensional ϕ - ψ (Ramachandran) map (Ramachandran and Sasisekharan 1968). All the major elements of protein secondary structures like the α -helix, β -sheet and reverse turn (β and γ) conformations lie within the allowed regions of the ϕ - ψ map. Upon incorporation of a second alkyl substituent at C α , as in Aib, the stereochemically allowed regions are severely limited, with the theoretically computed energy minima lying in the left and right handed $3_10/\alpha$ -helical regions of the conformational map ($\phi \sim \pm 60^\circ \pm 20^\circ$, $\psi \sim \pm 30^\circ \pm 20^\circ$) (figure 1). The expectation that Aib residues largely favour helical conformations has been borne out by the results of a large number of crystal structure investigations, (summarized partially in figure 1) which have been reviewed elsewhere (Prasad and Balaram 1984; Toniolo *et al* 1983). Extensive spectroscopic studies of Aib containing oligopeptides suggest that sequences of the type -(Aib) $_n$ - and -(Aib-X) $_n$ -adopt largely 3_10 -helical conformations stabilized by intramolecular 4 $\rightarrow$ 1 hydrogen bonds (Nagaraj *et al* 1979; Venkatachalapathi and Balaram 1981; Nagaraj and Balaram 1981b; Iqbal and Balaram 1981a, b, c 1982a, b; Vijayakumar and Balaram 1983a, b). Evidence for the formation of α -helical structures by Aib containing peptides, which contain other L-amino acids interspersed in the sequence, has come from single crystal x-ray diffraction studies of the 11-residue peptide, Boc-(Ala-Aib) $_2$ -Ala-Glu(OBzl)-(Ala-Aib) $_2$ -Ala-OMe (Butters *et al* 1981) (figure 2) and the 20-residue natural peptide, alamethicin (Fox and Richards 1982). However, 3_10 helix formation has been noted in the crystal structure of the decapeptide, Boc-Aib-Pro-Val-Aib-Val-Ala-Aib-Ala-Aib-Aib-OMe (Francis *et al* 1983) (figure 2). While the tendency of Aib containing sequences to favour helical folding has been established beyond doubt, the role of sequence and environmental effects in determining the precise nature of the helical structure (3_10 or α) remains to be elucidated. Thus, sequences rich in Aib can be used to generate helical oligopeptide conformations. It should however be noted that sidechain distributions differ in the 3_10 and α -helical conformations, with the former being characterized by 2 residues per turn

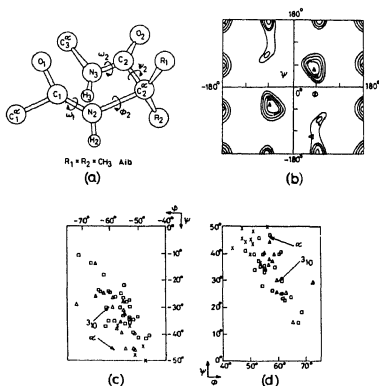


Figure 1. (a) Definition of conformational angles for Acetyl-Aib-N-methylamide. (b) Potential energy map for the Aib residue. Contours are drawn at 1 kcal mol^{-1} intervals with respect to the innermost contour enclosing the minimum. The ideal 3_{10} (■) and α - (▲) helical conformations are marked. ● represent crystal structure observations of Aib in non-helical conformations. (c, d) Crystallographic observations for Aib residues in peptides in the right (c) and left (d) handed helical regions. Tips of arrows indicate ideal 3_{10} and α -helices. Δ N-terminal residue in protected peptides. □ Non-terminal residue X C-terminal Aib present as ester or acid.

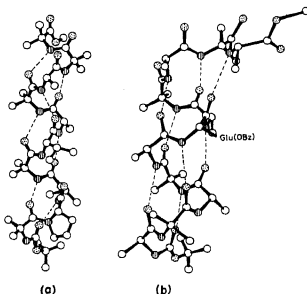


Figure 2. 3_{10} - and α -helical structures observed in Aib peptide crystal structures. (a) Boc-

of the helix, while the latter has 3.6 residues per helical turn (Ramachandran and Sasisekharan 1968).

2.2 β -turn conformations

Aib and Pro residues have a marked tendency to stabilize β -turn structures, in which the direction of peptide chain propagation is reversed, with two residues occupying the pivotal corner positions. β -turns have been classified into several types, differing in the ϕ , ψ values for the corner residues (Venkatachalam 1968). The ϕ value for a residue in the corner position of types I, II and III β -turns is constrained to $\sim -60^\circ$. This is the preferred region for Aib, while in L-Pro the constraints of cyclization imposed by the pyrrolidine ring, necessarily limit ϕ_{Pro} to values of $\sim -60^\circ \pm 15^\circ$. The formation of specific β -turn conformations by Aib and Pro containing peptides has been exemplified in several crystal structures (Prasad and Balaram 1983, 1984). ^1H NMR, CD and IR studies in solution suggest that these folded conformations are, in fact, retained in solution. For the -Pro-Aib-sequence, which is an almost obligatory β -turn sequence, it has been shown that both types II and III β -turns are energetically accessible. The type II structure ($\phi_{\text{Pro}} = -58^\circ$, $\psi_{\text{Pro}} = 139^\circ$, $\phi_{\text{Aib}} = 61^\circ$, $\psi_{\text{Aib}} = 25^\circ$) has been detected in the solid state for Piv-Pro-Aib-NHMe (Prasad *et al* 1982), while the type III structure ($\phi_{\text{Pro}} = -59^\circ$, $\psi_{\text{Pro}} = -34^\circ$, $\phi_{\text{Aib}} = -62^\circ$, $\psi_{\text{Aib}} = -18^\circ$) is observed in the cyclic disulphide, Boc-Cys-Pro-Aib-Cys-NHMe (Ravi *et al* 1983). Circular dichroism and



nuclear Overhauser effect studies suggest, that in solution both structures can be populated depending upon the solvent conditions (Rao *et al* 1983; Crisma *et al* 1983). The body of available results suggests that Aib-Pro and Pro-Aib sequences can be used to generate reverse turns in acyclic peptides with a considerable degree of certainty.

2.3 β -sheet conformations

Both parallel and antiparallel β -sheet structures are observed in proteins (Richardson 1981). However, there have been few attempts to generate models for these structures using synthetic peptides. The associated β -sheet structures have been exclusively studied using linear homooligopeptide models (Toniolo 1977). However, the precise nature of the associated species remains to be established, in these cases. It would therefore, be desirable to establish criteria for the design of peptides, folded to generate an antiparallel β -sheet conformation as illustrated in figure 3. In choosing a synthetic target it would be desirable to incorporate a sequence, which nucleates a β -turn (hairpin bend) or γ -turn in the centre of the peptide and to incorporate residues, which favour extended β -sheet conformations. With this end in view a series of peptides of the type Boc-(Val) $_n$ -Aib-Pro-(Val) $_m$ -OMe ($n = 2, 3$ and $m = 3$), Boc-(Val) $_n$ -X-(Val) $_m$ -OMe ($X = \text{Aib, Pro; } n = 2, 3$ and $m = 3$), have been synthesized. The Aib-Pro sequence was chosen to ensure chain reversal by β -turn formation, while the introduction of a single Aib or Pro residue in an oligo-Val sequence might favour γ -turn formation (figure 3). Val containing sequences were chosen in view of the propensity of this residue to occur in β -sheet conformations (Chou and Fasman 1978). Figure 4 shows the CD spectra of Boc-(Val) $_2$ -Aib-Pro-(Val) $_3$ -OMe in different solvents. The appearance of a negative CD band at 224 nm in dioxane is suggestive of a β -sheet conformation (H. Balaram

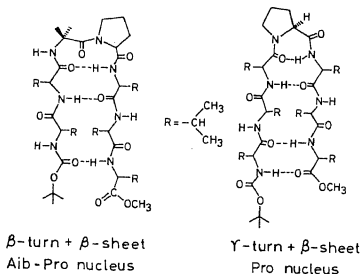


Figure 3. Possible nucleation of β -sheet conformations. Speculative conformations for Boc-(Val)₂-Aib-Pro-(Val)₃-OMe and Boc-(Val)₃-Pro-(Val)₃-OMe.

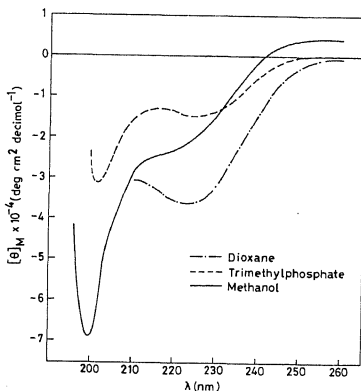


Figure 4. CD spectra of Boc-(Val)₂-Aib-Pro-(Val)₃-OMe in different solvents.

conformational flexibility. Further spectral studies, presently in progress, should allow the delineation of the conformational features of these putative β -sheet model peptides.

2.4 Covalent constraints introduced by disulphide bridging

Disulphide crosslinks can be introduced into peptides to stabilize specific chain conformations. In developing this approach cyclic and acyclic cystine peptides have been synthesized. Peptides of the type Boc-Cys-Pro-X-Cys-NHMe (X = Gly, L-Ala,

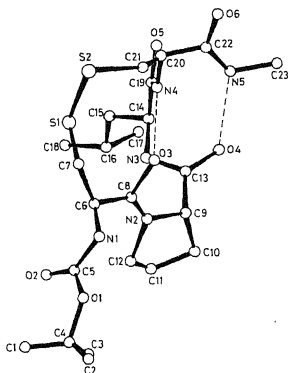
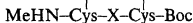


Figure 5. Solid state conformation of Boc-Cys-Pro-Leu-Cys-NHMe.

D-Ala, Aib, Leu, Val, Phe) provide rigid models for β -turn structures. Detailed spectroscopic (^1H , ^{13}C , NMR, IR, CD, Raman) studies have unambiguously established these peptides as β -turn structures (Ravi *et al* 1983; Ravi and Balaram 1984; Rao *et al* 1983; Ishizaki *et al* 1981; Venkatachalapathi *et al* 1982). Crystallographic studies on the X = Leu (Prasad, unpublished) and Aib peptides (Ravi *et al* 1983) demonstrate that a consecutive β -turn or an incipient, disulphide bridged, 3_{10} -helix occurs in both peptides in the solid state. Figure 5 illustrates the solid state conformation of the Pro-Leu cyclic disulphide.

Bis-cystine peptides of the type Boc-Cys-X-Cys-NHMe



(X = L-Ala, D-Ala, Gly, L-Leu) have been shown to adopt anti-parallel β -sheet conformations stabilized by two S-S crosslinks, located on the same face of the sheet (figure 6a). These peptides are characterized by unusually low field shifted Cys C^αH resonances in ^1H NMR spectra of CDCl_3 solutions, high $J_{\text{HNC}^\alpha\text{H}}$ values (~ 9 Hz) and extremely solvent shielded X-NH and $-\text{NHCH}_3$ resonances (Ravi 1983; Kishore unpublished results). From the conformation depicted in figure 6a, it is seen that the bis-cystine cyclic systems could serve as a starting point for designing peptide cavities, lined by sulphur atoms. Cystine can also be used to stabilize the antiparallel β -sheet conformation in acyclic sequences. In this connection, symmetrical peptides of the type Boc-Ala-Gly-Cys-Leu-Phe-OMe

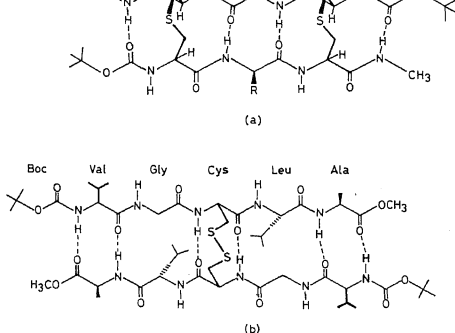


Figure 6. (a) Proposed conformation for the cyclic bis-cystine peptides. (b) Probable antiparallel β -sheet conformation in the peptide Boc-Val-Gly-Cys-Leu-Ala-OMe

Boc-Val-Gly-Cys-Leu-Ala-OMe

have been synthesized. Preliminary ^1H NMR measurements indicate extensive aggregation, as evidenced by line broadening. The conformation likely to be preferred is shown in figure 6b (Raj, unpublished results).

3. Design of bioorganic models

3.1 Retinylidene-lysine peptides as models for the bacteriorhodopsin chromophore

The protein bacteriorhodopsin constitutes the major protein of the purple membrane of *Halobacterium halobium* and is involved in the conversion of photon energy into a transmembrane electro-chemical H^+ gradient (Stoeckenius and Bogomolni 1982; Stoeckenius 1980). The retinal chromophore is attached *via* a Schiff base linkage to Lys-216, which lies in a membrane spanning helical segment of the protein (Stoeckenius and Bogomolni 1982). The absorption spectrum of the protein has a band at ~ 560 nm, which has been ascribed to a protonated Schiff base (PRSB) chromophore. However, this band is considerably redshifted as compared to model PRSB's obtained from retinal and model amines, leading to the suggestion that the spectral shift (opsin shift), is a result of the environmental effects due to proximate protein residues (Nakanishi *et al* 1980).

In an attempt to evaluate neighbouring group effects the peptides Boc-Aib-Asp-Aib-Aib-Lys-Aib-OMe and Boc-Aib-Asp-Aib-Ala-Aib-Lys-Aib-OMe have been synthesized. The choice of $(\text{Aib-X})_n$ sequences compels 3_{10} helical folding, thereby bringing the Asp and Lys residues within a reasonable distance for interaction. Figure 7 illustrates the disposition of residues assuming an ideal 3_{10} helical geometry for the peptide backbone. Table 1 summarizes the λ_{max} values obtained for the retinylidene peptides in

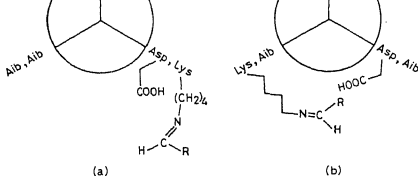


Figure 7. Helical wheel representations of peptides Boc-Aib-Asp-Aib-Aib-Lys-Aib-OMe (a) and Boc-Aib-Asp-Aib-Ala-Aib-Lys-Aib-OMe (b), in an ideal 3_{10} helical conformation. In (a) the Lys and Asp residues lie adjacent on the same face of the helix. In (b) the Asp and Lys residues lie on different faces with the Lys residue being translated by one turn of the helix.

protonated and unprotonated forms in different solvents. The results in solvents like $CHCl_3$ and CH_2Cl_2 suggest that the proximal Asp residue may stabilize the PRSB ground state by hydrogen bonding, in poorly solvating media thereby reducing the magnitude of the protonation red shift (Vijayakumar and Balaram 1984). These results suggest that a detailed examination of the effect of proximate residues is indeed possible, using the Aib-X sequences to provide a rigid helical scaffolding.

3.2 Models for binding sites on proteins: Bilirubin and gossypol

Proteins often interact with small molecules by specific multipoint interactions involving electrostatic, hydrogen bonding and hydrophobic effects. We have chosen to design peptide binding sites for the acyclic tetrapyrrole pigment, bilirubin and the phenolic triterpene gossypol (figure 8). Bilirubin, a degradation product of heme, is an extremely important metabolite involved in a variety of disease states (Berthelot *et al* 1982). The pigment has a strong affinity for serum albumins and binds noncovalently to a high affinity site on the protein (Brodersen 1982). The hydrophobic nature of this site and the involvement of charged residues like Lys and Arg have been inferred from several biochemical studies (Jacobsen 1975, 1977). Gossypol is acquiring increasing importance as a male antifertility agent (Quian *et al* 1980), in addition to possible uses against herpes virus (Wichmann *et al* 1982) and in the treatment of malaria (Vander Jagt *et al* 1982). This binaphthyl derivative has been isolated in the racemic ($\pm$) form from cottonseed oil (Abou Donia 1976) and in optically active (+) form from the bark of the tree *Thespesia populnea* (Datta *et al* 1968; King and De Silva 1968). A resolution of optical isomers (atropoisomers) has not been effected and (–) gossypol is, as yet, unavailable for biological studies. Gossypol inhibits a variety of nucleotide binding enzymes, of which its specific inhibition of the lactate dehydrogenase of sperm (LDH-X) is of special interest (Olgiati and Toscano 1983). It has also been shown to bind to serum albumins and glutathione-S-transferases, at the same site as bilirubin (Royer and Vander Jagt 1983; Vander Jagt *et al* 1983). The presence of two aldehyde groups on gossypol suggests that bifunctional attachment to a protein *via* Schiff base formation, involving two proximal Lys residues is an attractive possibility.

Table 1. Absorption band positions for retinylidene peptides^(a) in various solvents.

Solvent	Peptide 1			Peptide 2			Peptide 3		
	SB $\lambda_{\max}$ (nm)	SBH ⁺ ^(b) $\lambda_{\max}$ (nm)	$\Delta\nu$ (cm ⁻¹)	SB $\lambda_{\max}$ (nm)	SBH ⁺ $\lambda_{\max}$ (nm)	$\Delta\nu$ (cm ⁻¹)	SB $\lambda_{\max}$ (nm)	SBH ⁺ $\lambda_{\max}$ (nm)	$\Delta\nu$ (cm ⁻¹)
Dimethylsulphoxide	357	435	5023	356	435	5101	355	439	5390
Methanol	358	446	5511	357	443	5438	357	444	5489
n-Octanol	361	443	5127	360	432	4501	357	439	5232
Ethylacetate	339	434	6457	347	433	5724	346	439	6123
Chloroform	337	410	5283	336	408	5252	336	460	8023
Dichloromethane	—	—	—	—	—	—	356	498	8010

^(a) Peptide 1 = Boc-Aib-Asp-Aib-Aib-Lys-Aib-OMe; Peptide 2 = Boc-Aib-Asp-Aib-Ala-Aib-Lys-Aib-OMe; Peptide 3 = Boc-Aib-Lys-Aib-OMe.

^(b) Protonation was effected by adding excess trichloroacetic acid (0.028 M).

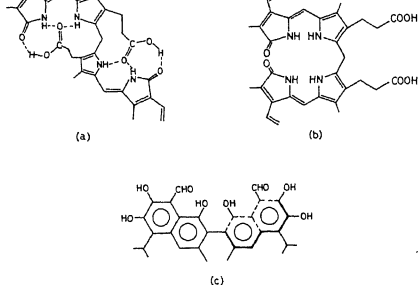


Figure 8. Extended (a) and folded (b) conformations of bilirubin IX- α . (c) Gossypol.

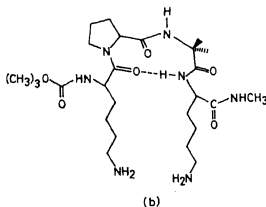
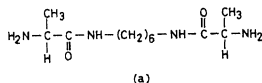


Figure 9. Structures of N,N' -bis-L-alanyl-hexamethylenediamine (a) and Boc-Lys-Pro-Aib-Lys-NHMe in a probable β -turn conformation (b).

We have therefore explored the possibility of developing diamines and di-Lys peptides as model receptors for both bilirubin and gossypol. Figure 9 illustrates the structures of two molecules that have been synthesized as a first step in this direction. Di-L-alanyl hexamethylenediamine is a chiral diamine and it was hoped that specific interactions with bilirubin could be monitored by induction of optical activity in the pigment (Blauer and Wagniere 1975). The CD spectra of bilirubin in the presence of HSA at pH 8.7 and with the chiral diamine in dioxane, are compared in figure 10. The

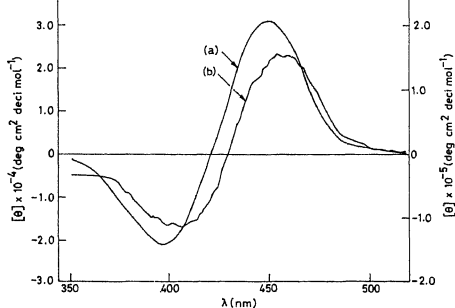


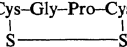
Figure 10. CD spectra of bilirubin in the presence of human serum albumin (HSA) and di-L-alanylnhexamethylene diamine. (a) HSA 3.46×10^{-5} M, bilirubin 3.46×10^{-5} M, pH 8.7, phosphate buffer. (b) Diamine 2.1×10^{-3} M, bilirubin 2.06×10^{-5} M, dioxane. Right scale is for trace (a). Left scale is for trace (b).

similarity of the signs of the CD bands at ~ 400 nm (negative) and ~ 450 nm (positive) suggests that the same helical twist of the dipyrromethene chromophores, is maintained in both cases. In contrast, entirely different CD spectra are generated in the presence of α -helical and β -sheet forms of poly-L-lysine in aqueous solution (Marrisey and Balaram 1984).

Figure 11 shows the CD spectrum of (+) gossypol in dioxane and the influence of the addition of the peptide Boc-Lys-Pro-Aib-Lys-NHMe. This peptide was chosen to permit β -turn formation at the Pro-Aib segment, thereby allowing the Lys residues the possibility of binding simultaneously to the two aldehyde moieties on gossypol. The dramatic changes in CD spectra suggest that this expectation has been realized. Further support for the bifunctional interaction comes from the lack of significant changes in (+) gossypol CD spectra in the presence of Ac-Lys-NHMe (Whaley *et al*, unpublished).

3 Models of protein active sites

Attempts to model the active sites of enzymes like proteases have thus far met with limited success (Schultz *et al* 1982). We have, therefore, chosen to develop models for redox sites, which are composed of small disulphide loops. Thioredoxin, an ubiquitous protein, is of great importance in a variety of cellular redox processes (Holmgren 1981a). The active site of the protein consists of the fourteen membered loop formed between Cys residues 32 and 35 (figure 12). Structural changes on reduction of the disulphide have been monitored by following the enhancement of Trp fluorescence (Holmgren 1981b). The peptides Boc-Cys-Gly-Pro-Cys-NHMe



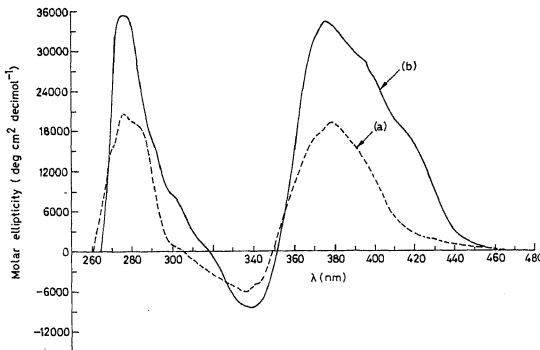


Figure 11. CD spectra of (+) gossypol and a peptide complex. (a) (+) Gossypol 6×10^{-6} in dioxane. (b) (+) Gossypol 6×10^{-6} M and 5×10^{-5} M Boc-Lys-Pro-Aib-Lys-NHMe dioxane.

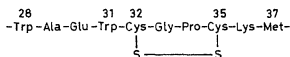
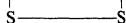
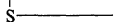


Figure 12. Partial sequence of *E. coli* thioredoxin in the vicinity of the active site.

and Boc-Trp-Cys-Gly-Pro-Cys-NHMe have been synthesized as models for the



thioredoxin active site. ^1H NMR and CD studies favour a consecutive β -turn conformation in the former (Ravi and Balaram 1983). Figure 13 shows the effect of disulphide reduction on the Trp containing peptide model. It is observed that the Trp fluorescence enhancement parallels that observed for the native protein (Kishore *et al* 1983). The active site peptide of the protein glutaredoxin (Holmgren 1981a), -Cys-Pro-Tyr-C



has also been synthesized and studies on the synthesis of the thioredoxin segment shown in figure 12 are underway (Kishore, unpublished). A comparison of the structural, spectroscopic and redox properties of these systems will be of value in elucidating further details of the molecular mechanisms involved at the redox active site in thioredoxin and related proteins.

4. Conclusions

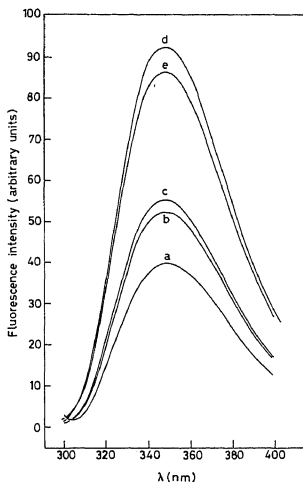


Figure 13. Fluorescence spectra of Boc-Trp-Cys-Gly-Pro-Cys-NHMe excited at 290 nm, in water. (a) Peptide (b) Peptide + dithiothreitol (DTT) 20 minutes after addition of reducing agent (c) 50 minutes after DTT addition. (d) L-Trp (e) L-Trp + DTT. Curves (d) and (e) represent controls.

bioorganic chemistry have been briefly illustrated. Of necessity, these have been limited to examples emanating from the author's laboratory. Significant obstacles remain in the synthesis of peptides containing more than one conformational domain and in the rational control of sidechain flexibility. There is little doubt that intensified activity in this area should rightfully position peptide chemistry as a central part of bioorganic chemistry.

Acknowledgements

This article reports the results of several of the author's coworkers, who have been cited in the references and in the text in the case of unpublished work. Research in this area has been funded by the Department of Science and Technology and the Department of Atomic Energy.

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Alcoholate derivatives of 3d transition metal chlorides

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Abstract. A brief account of the work carried out on the title compounds in our laboratories during the last few years is presented in the perspective of existing knowledge on the topic.

Keywords. Alcoholates of scandium; titanium; vanadium; chromium; manganese; iron; cobalt and nickel chlorides; electronic spectra; ESR spectra; magnetic susceptibilities; thermogravimetric studies.

1. Introduction

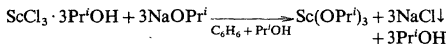
Although alcoholate complexes of transition metal chlorides have been known (Mellor 1931) for more than a century, a few physicochemical studies on these have been carried out only during the last decade or so. In view of these alcoholate complexes being used more and more as catalysts in organic polymerization reactions and as starting materials for the synthesis of metal alkoxides, a brief review of the existing knowledge of their synthesis and physicochemical properties is presented in this article.

2. Synthetic studies

The general method employed for the synthesis of alcoholate complexes of metal chlorides is the addition of alcohols directly to the anhydrous metal chlorides. A modification of the method can be illustrated by the preparation of ethanol adducts of chlorides of nickel(II), manganese(II) and cobalt(II) by passing chlorine gas in a suspension of the powdered metal in ether and alcohol (Osthoff and West 1954). Another modification of the method is to take a suitable adduct like $\text{CrCl}_3 \cdot 3\text{THF}$ which reacts with alcohols resulting in the formation of adducts much more readily than the anhydrous chloride itself (Mahendra *et al* 1977). The more covalent metal chlorides undergo substitution, instead of simple adduct formation reactions with the formation of chloride alkoxides, which in turn form adducts, *e.g.* $\text{TiCl}_2(\text{OC}_2\text{H}_5)_2 \cdot \text{C}_2\text{H}_5\text{OH}$ (Jennings *et al* 1936). The primary alcohols generally give the most stable adducts, but the stability decreases with the chain length. Tertiary alcohols, on the other hand, give the least stable adducts which even under mild conditions tend to decompose yielding tertiary alkyl chloride and hydrolysed metal chloride. A brief description of the synthesis of alcohol adducts of chlorides of $3d^1$ to $3d^8$ metals is presented in the following paragraphs.

Scandium trichloride resembles lanthanon chlorides (Mehrotra and Batwara 1970) in forming stable tris-alcoholates with primary and secondary alcohols, but with tertiary alcohols unstable lower alcoholates, *e.g.* $\text{ScCl}_3 \cdot 1.5\text{Bu}'\text{OH}$ is obtained

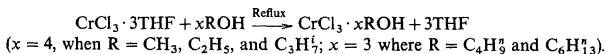
$\text{ScCl}_3 \cdot 3\text{Pr}^i\text{OH}$ has been shown (Mehrotra 1972) to serve as a very suitable material for the preparation of $\text{Sc}(\text{OPr}^i)_3$ by the reaction:



Titanium(III) chloride reacts with alcohols to give products of the type $\text{TiCl}_3 \cdot 4\text{ROH}$ (where $\text{R} = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7^i, \text{C}_4\text{H}_9^s$ etc.) (Gibbenbach and Brubaker 1968; Schlafer and Gotz 1964). Titanium tetrachloride reacts with ethanol or isopropanol to give products of the type $\text{TiCl}_2(\text{OR})_2 \cdot \text{ROH}$ (where $\text{R} = \text{Et}, \text{Pr}^i$) (Jennings *et al* 1936). The reaction of TiCl_4 with Bu^nOH in the presence of sunlight yields (Hunt and Winter 1970) $\text{TiCl}_3 \cdot 3\text{Bu}^n\text{OH}$.

Vanadium trichloride reacts with lower alcohols (Bradley and Mehta 1962; Casey and Clark 1969) like methanol and isopropanol to give products of the type $\text{VCl}_3 \cdot 4\text{ROH}$, whereas ethanol forms 1:3 complex as $\text{VCl}_3 \cdot 3\text{EtOH}$. Vanadium tetrachloride on the other hand (Bradley *et al* 1958) reacts with alcohols in cold benzene forming the dichloride dialkoxide alcoholates $\text{VCl}_2(\text{OR})_2 \cdot \text{ROH}$ (where $\text{R} = \text{Me}, \text{Et}, \text{Pr}^n, \text{Pr}^i, \text{Bu}^n, \text{Bu}^i, \text{Bu}^s$ and Am^n). Under more vigorous conditions especially with tertiary alcohols, hydrolytic side reactions occur.

The preparation of $\text{CrCl}_3 \cdot x\text{ROH}$ ($x = 3$ or 4) was reported by Kandelaki (1937) and it was claimed that the adduct $\text{CrCl}_3 \cdot 4\text{ROH} \cdot \text{R}_2\text{AlCl}$ is in many cases better Zeigler-Natta catalyst (Michio *et al* 1969) than the conventional $\text{TiCl}_4 \cdot \text{R}_3\text{Al}$. In a recent study (Mahendra *et al* 1977) the purple-coloured adduct of chromium chloride with tetrahydrofuran, $\text{CrCl}_3 \cdot 3\text{THF}$ (prepared by refluxing $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ in THF in the presence of thionyl chloride) has been found as a much more convenient starting material for the preparation of alcoholates as it is soluble in alcohols whereas anhydrous CrCl_3 is insoluble. Solvolytic reactions of $\text{CrCl}_3 \cdot 3\text{THF}$ in excess of alcohols under strictly anhydrous conditions lead to the formation of complexes of the type $\text{CrCl}_3 \cdot x\text{ROH}$, the reactions may be depicted as follows:

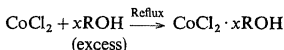


As the alcoholates formed in solutions could not be crystallized, these were isolated by distilling out the excess solvent (parent alcohol), followed by drying the product under reduced pressure at a suitable temperature depending upon the boiling point of alcohol. The apparent difference in the number (4 and 3) of molecules of added alcohol for the alcoholates mentioned above may, therefore, be due to the higher temperatures employed for removal of excess alcohols in the latter alcoholates. With tertiary alcohols, hydrolytic side reactions occur in the case of $\text{CrCl}_3 \cdot 3\text{THF}$ also as reported in the case of vanadium tetrachloride.

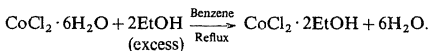
Alcoholate derivatives with anhydrous manganese chloride have been reported with the composition $\text{MnCl}_2 \cdot x\text{ROH}$ (where $x = 1 - 2$; $\text{R} = \text{Me}, \text{Et}, \text{Pr}^n, \text{Pr}^i, \text{Bu}^n, \text{Bu}^i, \text{Bu}^s, \text{Bu}^t, \text{Am}^n, \text{Am}^i$ and Hex^n) (Mehrotra and Aggarwal 1984). It was further observed that primary alcohol adducts were highly soluble in parent alcohols while solubility of adducts was lesser in secondary and much lesser in tertiary alcohols. No hydrolytic reactions could be discerned in these derivatives.

propylⁿ, propylⁱ, butylⁿ, butylⁱ and pentylⁿ alcohol with ferric chloride (Multani 1956). These can be represented by the general formula, $\text{FeCl}_3 \cdot 2\text{ROH}$, where $\text{R} = \text{Me}$, Pr^n , Pr^i , Bu^n , Bu^i and pentylⁿ groups. The higher alcoholates were also prepared from diethyl and diisopropyl alcohols by alcohol interchange method. Anhydrous ferrous chloride reacts with methyl, ethyl, propylⁿ, and propylⁱ alcohols to give compounds which also conform to the general formula, $\text{FeCl}_2 \cdot 2\text{ROH}$ (Jain and Multani 1966). The higher alcoholates could not be prepared by alcohol interchange methods as the complexes got oxidized to the ferric state (Bradley *et al* 1958).

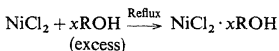
A bis-ethanol adduct, $\text{CoCl}_2 \cdot 2\text{C}_2\text{H}_5\text{OH}$ was reported by Lloyd *et al* (1928) on the basis of chloride analysis. In a recent study (Singh *et al* 1980), crystalline adducts with the general formula, $\text{CoCl}_2 \cdot x\text{ROH}$ have been isolated either by crystallisation or by distilling off the solvents from the clear solutions obtained by dissolving anhydrous CoCl_2 in different alcohols:



(where $\text{R} = \text{Me}$, Et , Pr^i , Bu^n , Bu^s , Bu^i ; $x = 2$; and $\text{R} = \text{Bu}^i$, $x = 1$). The methanolate, ethanolate and isopropanolate adducts of CoCl_2 could be crystallized and were, therefore, obtained by drying the crystalline products under reduced pressure. These alcoholate derivatives are blue (except methanolate which is light pink) coloured solids. These are insoluble in common organic solvents other than in alcohols. The ethanolate adduct has also been isolated by the reaction of hydrated CoCl_2 with ethanol in benzene medium, removing the water azeotropically:

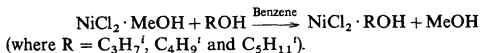


A number of ethanolate complexes of nickel chloride, $\text{NiCl}_2 \cdot x\text{C}_2\text{H}_5\text{OH}$ (where $x \leq 4$) were described by Ward (1972) at different temperatures. The bis-ethanol compound described by Osthoff and West (1954) could not be isolated by Ward, but he has reported thermogravimetric evidence of its existence. In a recent detailed study (Baranwal and Mehrotra 1978), a number of alcoholates of nickel chloride with different primary alcohols have been described:



(where $\text{R} = \text{CH}_3$, C_2H_5 , C_3H_7 , C_4H_9 , C_6H_{13} and C_8H_{17} and $x = 1-4$).

Anhydrous nickel chloride dissolves in primary alcohols on refluxing and from the clear green solutions thus obtained greenish yellow adducts with the formula $\text{NiCl}_2 \cdot x\text{ROH}$ ($x = 2-4$) have been isolated by removal of the solvent. On drying the products further under reduced pressure (2.5 mm) at a temperature (32 to 120°C) corresponding to the boiling point of alcohol (CH_3OH to $\text{C}_8\text{H}_{17}\text{OH}$), yellow products corresponding in composition to $\text{NiCl}_2 \cdot \text{ROH}$ are obtained. Anhydrous nickel chloride, however, does not appear to dissolve in or react with secondary and tertiary alcohols and appears to remain unaffected when refluxed with these. Adducts with such alcohols could, however, be prepared by alcohol interchange technique which can be depicted as follows:



The liberated methanol could be azeotroped out with benzene and the products dried under reduced pressure. These adducts are also yellow-coloured compounds but in contrast to the adducts with primary alcohols, these are insoluble in parent alcohols. This insoluble behaviour may be explained on the basis of lower polarity of secondary and tertiary alcohols compared to the primary ones and the steric hindrance to solvation by addition of further alcohol molecules to the secondary and tertiary alcohol adducts. The formation of higher alcohol adducts of the type, $\text{NiCl}_2 \cdot x\text{ROH}$ (where $x > 1$) and ($\text{R} =$ primary alkyl group) is confirmed by the exothermic reaction with change in colour from yellow to green on dissolution of mono-alcohol adducts in the primary alcohols.

3. Physicochemical studies

3.1 Infrared spectra

Infrared spectra of all the alcoholate complexes are almost similar. A broad and strong absorption band observed at $\sim 3080 \text{ cm}^{-1}$ in all the metal chloride complexes is assigned to ν_{OH} . In pure alcohols, this band appears at $\sim 3300 \text{ cm}^{-1}$ and the lowering can be explained to arise from the coordination of the alcohol molecule to the central metal atom (Nakamoto 1970).

3.2 Electronic spectra

In the case of vanadium(III) (Casey and Clark 1969), the two accessible spin-allowed $d-d$ transitions for an octahedrally coordinated d^2 species are assigned as ${}^3T_{1g} \rightarrow {}^3T_{2g} (F)$ at lower energy (ν_1) and ${}^3T_{1g} (F) \rightarrow {}^3T_{1g} (P)$ at higher energy (ν_2). For the chloride alcoholates of vanadium(III), ν_1 occurs in the range 14000 to 14900 cm^{-1} with a shoulder on the low frequency side. The shoulder arises from the resolution of the ${}^3T_{2g}$ term by low symmetry components; these are undoubtedly present, owing to the non-equivalence of the six ligands attached to the metal atom. The second band, ν_2 occurs in the range 21050 – 22050 cm^{-1} . The methanol complex gives rise to the highest values for both ν_1 and ν_2 and there is a general trend for both bands to move progressively to lower energies with higher alcohols. This implies that higher alcohols have slightly lower ligand field strengths than methanol. The band maxima and the extinction coefficients for the methyl, ethyl and isobutyl alcohol solutions agree closely with those originally reported by Hartmann and Schlafer (1951).

The ligand field strengths of the alcohols fall in the order $\text{CH}_3\text{OH} > \text{C}_2\text{H}_5\text{OH} > \text{C}_3\text{H}_7^i\text{OH} > \text{C}_4\text{H}_9^i\text{OH} > \text{C}_3\text{H}_7^i\text{OH} > \text{C}_4\text{H}_9^i\text{OH} > \text{C}_4\text{H}_9^s\text{OH}$. Steric hindrance of the branched alcohols probably contributes to their lowering ligand field strengths. The lower ligand field strength of the $\text{V}(\text{C}_3\text{H}_7^i\text{OH})_4\text{Br}_2^+$ ion compared with the corresponding chloro ion is consistent with the relative positions of bromide and chloride in the spectrochemical series.

The electronic spectra of all the chromium complexes in parent alcohols are identical with their diffuse reflectance spectra and so it is evident that no immediate structural

15000 cm^{-1} (v_1) and 20500 cm^{-1} (v_2) to the $^4A_{2g} \rightarrow ^4T_{2g}$ and $^4A_{2g} \rightarrow ^4T_{1g}$ (F) transitions respectively. The first transition $^4A_{2g} \rightarrow ^4T_{2g}$ represents 10 Dq for a d^3 system in an octahedral field. The observed transitions show that the ligand field value increases as the polarity of the alcoholic group increases (in the case of primary alcohols). The interelectronic repulsion parameters in all cases are much lower than that (1030 cm^{-1}) observed for the free ion showing considerable covalent nature of the metal ligand bond in these alcoholate derivatives.

The spectra of alcoholates of manganese chloride have been recorded in concentrated solutions (Mehrotra and Aggarwal 1984) but extremely weak transitions are observed in these cases. Only a single transition ($\sim 29600 \text{ cm}^{-1}$) could be observed in case of tertiary butanol derivative while other derivatives exhibited comparatively stronger absorptions in the visible region (19000–32900 cm^{-1}). These values are indicative of tetrahedral geometry in all these cases with the exception of methoxy derivative which exhibited spectra nearer to an octahedral geometry (Figgis 1976).

The spectrum of $\text{CoCl}_2 \cdot 2\text{MeOH}$ shows two well-defined bands with maxima at 18590 and 14790 cm^{-1} . The third band at 7550 cm^{-1} is observed for this compound in the near-infrared region. These bands are characteristic for Co(II) in octahedral environment of this compound and can be assigned to the following transitions:

$$\begin{aligned} 7550 \text{ cm}^{-1}; & \quad ^4T_{1g} \rightarrow ^4T_{2g} (v_1), \\ 14790 \text{ cm}^{-1}; & \quad ^4T_{1g} \rightarrow ^4A_{2g} (v_2), \\ 18590 \text{ cm}^{-1}; & \quad ^4T_{1g} \rightarrow ^4T_{1g} (P) (v_3). \end{aligned}$$

The visible spectrum of this compound is also similar to the spectra (Figgis 1976) of $\text{Co}(\text{H}_2\text{O})_6^{2+}$ and $\text{Co}(\text{OMe})_2$ in which also Co^{2+} ions are present in octahedral environment. With the help of these three transitions, the values of spectroscopic parameters, *e.g.* 10 Dq; interelectronic repulsion parameter (B) and covalency factor (B) have been calculated as 7600 cm^{-1} , 845 cm^{-1} and 0.87 respectively.

However, the visible spectra of all other alcoholate derivatives, $\text{CoCl}_2 \cdot x\text{ROH}$ (where $x = 2$, $\text{R} = \text{Et}$, Pr^i , Bu^n , Bu^s , and Bu^t ; when $x = 1$, $\text{R} = \text{Bu}^i$) when recorded in parent alcohols gave a band towards higher energy side in the range $14850 \pm 150 \text{ cm}^{-1}$. The near-infrared bands for all these derivatives have been observed in the range $6325 \pm 125 \text{ cm}^{-1}$. These transitions are characteristic for Co(II) in tetrahedral environment (Lever 1968) and can be assigned transitions as $(v_3)^4A_2 \rightarrow ^4T_1$ (P) and $v_2^4A_2 \rightarrow ^4T_1$ (F) respectively. The intense blue colour of these derivatives also supports the above view that Co^{+2} ions are also present in tetrahedral geometry in these compounds. It has been observed that the values of B calculated from the observed spectra for all the alcoholate derivatives of CoCl_2 are lower than the free ion value (1120 cm^{-1}) for Co^{2+} in $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, indicating a higher covalent nature of the alcoholates.

The spectra of the monoalcoholate adducts of nickel exhibit three bands around 7000–8000 cm^{-1} (v_1); 12000–14000 cm^{-1} (v_2) and 21000–24000 cm^{-1} (v_3) which indicate a pseudooctahedral geometry for the complexes (Goodgame *et al* 1964; Lever *et al* 1965; Baranwal and Mehrotra 1978). The spectral behaviour of the complexes in solid phase is almost identical with that in solution. This indicates that there is no change in geometry when the complexes are taken in solution and they retain their geometry in solid state also. Various spectroscopic parameters like ligand field splitting energy (10 Dq), interelectronic repulsion parameter (B) and β have also been calculated

from these transitions. The 10^4 values show that the strength of the ligand field decreases with higher alcohols, which is in agreement with the trend expected from the variation in the polarity of alcohols. The B values in all these alcoholate derivatives are below the free ion value (1040 cm^{-1}) for $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ showing considerable covalent nature of the metal-ligand bond.

The most interesting spectral feature of these complexes is the triplet structure of the ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$ band. The excited state concerned corresponds to the configuration $(t_{2g})^4 \rightarrow (e_g)^4$. The triplet structure, therefore, shows non-equivalence of $3d$ orbitals (d_{xy} , d_{yz} , d_{zx}). A rhombic symmetry of the ligand field with μ_x , μ_y and μ_z may be inferred, where μ_x , μ_y and μ_z represent the sum of the charges on the x , y and z axis respectively.

3.3 Conductivity measurements

The equivalent conductances of vanadium trichloride in various alcohols was measured (Casey and Clark 1969) at three concentrations in each case and compared with that of triethylammonium chloride in the same alcohol at comparable concentrations. Treatment of the conductivity results by the method outlined by Feltham and Hayter (1964) leads to the conclusion that the vanadium species in solution are 1:1 electrolytes.

Conductivity measurements (Mahendra *et al* 1977) of alcoholate complexes of CrCl_3 reveal them to be weak electrolytes in parent alcohols (Dubicki *et al* 1968).

The molar conductance ($\lambda_m = 170.9 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$) of $\text{CoCl}_2 \cdot 2\text{MeOH}$ solution in methanol (Singh *et al* 1980) indicates that it behaves as 1:2 electrolyte (Khan 1975) which may be represented by the formula: $[\text{Co}(\text{MeOH})_6]^{2+} \cdot 2\text{Cl}^-$. The ethanolate derivative $\text{CoCl}_2 \cdot 2\text{EtOH}$ in ethanol solution appears to behave as 1:1 electrolyte ($\lambda_m = 47.8 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$) whereas the isopropanolate derivative in isopropanol appears to be weak electrolyte ($\lambda_m = 1.3 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$). The other alcoholate derivatives behave as non-electrolytes in parent alcohols, which may be partly due to decreasing value of dielectric constants of the solvents.

The molar conductivities of nickel chloride methanolate and ethanolate derivatives in methanol and ethanol have been found to be 145 and $122 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$ respectively (Baranwal and Mehrotra 1978). These values correspond to the values expected for 1:2 electrolytes (Hussain and Rehman 1978) in these solvents and hence, the species in solution appears to be $[\text{Ni}(\text{ROH})_x]^{2+} \cdot 2\text{Cl}^-$. In view of the prominent tendency of nickel to show coordination state six, the value of x in the above moieties may also be six.

3.4 Thermogravimetric studies

In the case of vanadium(IV) chloride it has been observed that on heating the dichloride diethoxide alcoholates at $158^\circ/0.1 \text{ mm}$, it formed vanadium oxychloride alkoxides $\text{V}_2\text{OCl}_3(\text{OR})_3$ (Bradley *et al* 1958) whereas in the case of vanadium(III) chlorides, a 1:4 complex of the type $\text{VCl}_3 \cdot 4\text{ROH}$ ($\text{R} = \text{CH}_3$, C_3H_7) and a 1:3 complex of the type $\text{VCl}_3 \cdot 3\text{ROH}$ ($\text{R} = \text{Et}$) are formed (Casey and Clark 1969).

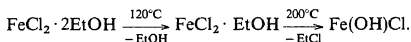
In the case of chromium as already mentioned (Mahendra *et al* 1977), the apparent difference in the number (4 and 3) of molecules of adduct alcohol in the two groups of alcoholates may be due to the higher temperatures employed for removal of excess alcohols in the latter cases. In order to test this hypothesis, a thermogravimetric study of

tetramethanolate and tetraethanolate which are obtained by drying at room temperature has been carried out.

It has been observed that tetraethanolate $\text{CrCl}_3 \cdot 4\text{EtOH}$ loses one molecule of ethanol at $\sim 65^\circ\text{C}$ forming an adduct corresponding in composition to $\text{CrCl}_3 \cdot 3\text{EtOH}$; the second and third molecules of added ethanol appear to be lost at $\sim 100^\circ\text{C}$ and 140°C respectively. After 140°C an extensive intramolecular reaction appears to take place, resulting finally in a compound with the composition $\text{Cr}(\text{OEt})\text{Cl}_2$ at about 200°C . An almost similar pattern of initial loss of adduct molecules followed by decomposition has been found with tetramethanolate, with the only difference that the tetramethanolate appears to be more stable to heat and the temperature required to remove the first mole of methanol is $\sim 120^\circ\text{C}$. When the alcoholate complexes (methanolate and ethanolate) are heated at $\sim 200^\circ\text{C}$ under atmospheric pressure for 1 hr, they appear to give a hydroxy- or oxy-product with the liberation of HCl gas which was estimated. The alcoholate complexes of ferrous chloride (Jain and Multani 1966) behave almost similar to chromium complexes (Mahendra *et al* 1977).

The thermogravimetric studies in case of manganese derivatives indicated that the products lose total alcohol molecules at about 300°C . It was observed that removal of alcohol molecules occurs at a temperature about $40\text{--}80^\circ\text{C}$ higher than their respective boiling points indicating that alcohol molecules get linked somehow with the metal ion (Mehrotra and Aggrawal 1984) *e.g.* in the case of $\text{MnCl}_2 \cdot 2\text{MeOH}$, the first methanol molecule was lost between 120 and 180°C while the second one is lost between 220 and 280°C after which the residue of manganese chloride only remained. Similar observations have been made in other derivatives also. These results are consistent with the studies made in the case of $\text{MnCl}_2 \cdot 2\text{EtOH}$ adduct (Osthoff and West 1954).

The diethyl alcoholate of ferrous chloride, $\text{FeCl}_2 \cdot 2\text{EtOH}$, when heated to 120°C loses a molecule of ethanol and the resulting compound on analysis was found to be ferrous chloride mono-alcoholate, $\text{FeCl}_2 \cdot \text{EtOH}$. When heating is continued to 200°C , ferrous hydroxy chloride is formed according to the following equation:



Nickel chloride tetramethanolate could be obtained (Baranwal and Mehrotra 1978) after drying the solution of NiCl_2 in methanol in the range $0\text{--}10^\circ\text{C}$ at 20 mm pressure. It lost one molecule of methanol at $20^\circ\text{C}/2.5$ mm, giving adduct of the formula $\text{NiCl}_2 \cdot 3\text{MeOH}$. The second and third molecules of added methanol appear to be lost at $\sim 30^\circ\text{C}$ and 45°C (2.5 mm) respectively. The mono adduct NiCl_2MeOH appears to be stable upto 70°C (2.5 mm). Further loss of methanol is slow and only 0.5 molecule of methanol appears to be lost in heating the mono-alcoholate to $140\text{--}150^\circ\text{C}$ (2.5 mm). Even a higher temperature ($\sim 250^\circ\text{C}$) is required to remove the remaining methanol from the adduct. An almost similar pattern of loss of adduct molecules has been found with nickel chloride tetraethanolate (Baranwal and Mehrotra 1978).

3.5 Magnetic moments

The magnetic moments of the solid alcoholate complexes of vanadium(III) chloride have been measured over the range ~ 300 to $\sim 80^\circ\text{K}$ (Casey and Clark 1969). In all cases, the magnetic moments fall with decreasing temperature in agreement with the

that predicted for an octahedrally coordinated d^2 ion and can be explained by the presence of axial distortions in the cubic field.

Magnetic moments of alcoholate complexes of chromium at room temperature in parent alcohols lie in the range typical for chromium(III), in an octahedral environment, with the observed values of magnetic moment close to the spin only value of 3.88 BM (Mahendra *et al* 1977).

Magnetic measurements on manganese derivatives indicated moments from 5.62 to 6.09 BM, which are indicative of spin free outersphere complex formation (Carlin and Duyneveldt 1977).

Experimental values reported (Figgis and Lewis 1964) for cobalt(II) derivatives in octahedral and tetrahedral geometries lie in the ranges of 4.7–5.2 and 4.4–4.7 BM respectively. Among the alcoholate derivatives studied during the present investigations (Singh *et al* 1980), only the methanolate adduct derivative shows a magnetic moment value of 4.85 BM, which corresponds to the range typical for octahedral geometry. Magnetic moments of other alcoholate derivatives lie in the range of 4.60 ± 0.08 BM which are suggestive of Co^{2+} ions in tetrahedral environment for these derivatives. Thus these magnetic studies also support the spectral interpretations of the alcoholate derivatives of CoCl_2 .

The magnetic moment values of nickel complexes at room temperature have been found to lie in the range 3.08–3.23 BM indicating octahedral geometry for nickel(II) (Baranwal and Mehrotra 1978). Calculations of spin-orbit coupling constants (λ) gave values in the range $155\text{--}275\text{ cm}^{-1}$ which are considerably lower than the free ion value of $\lambda = -324\text{ cm}^{-1}$, indicating covalent character of the metal ligand bond in these complexes.

3.6 ESR spectra

ESR spectra of only a few alcoholate complexes of transition metal halides like chromium(III), manganese(II) and nickel(II) have been carried out recently.

A chromium(III) complex of perfect octahedral symmetry is expected to show ESR signals centred around g value (Lande splitting factor) less than the free electron value (2.0023), the lowering being related to the covalent character of the metal ligand bond (Goodman and Raynor 1970). ^{53}Cr hyperfine structure and donor atom superfine splitting may also be observed. At room temperature, all the alcoholate derivatives in polycrystalline state give one signal in their spectra enabling a precise evaluation of g values. The data show that g values decrease from ethanolate to isopropanolate to normal butanolate, with the methanolate showing exceptionally low values. These values are all below the free electron values as expected. Assuming a similarity in the nature of Cr–Cl bond in all the complexes under discussion, the above data indicate a higher covalent character of the metal-ligand bond. The spectra in alcoholic solutions are generally much better defined and are almost similar to the spectra recorded for polycrystalline forms.

The manganese derivatives gave values of g ranging from 1.997 to 2.003 indicating a symmetrical structure around metal ion during their studies in the polycrystalline solid state at room temperature (Carlin and Duyneveldt 1977) and support the earlier discussed proposed structures.

In the case of nickel, room temperature ESR spectra of all these derivatives in the polycrystalline form show one signal from which the values of Lande splitting factor g

have been calculated (Baranwal and Mehrotra 1978). The g values lie in the range 2.03–2.44 which is expected for a nickel atom in an octahedral field.

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Role of orbital symmetry in transition metal promoted ring opening reactions of methylenecyclopropanes and cyclobutenes

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Abstract. Transition metals catalyse a variety of organic reactions, of which the ring opening of strained ring organic molecules generated a lot of interest. Theoreticians predicted a metal orbital catalysed pathway, which involved concerted bond breaking and bond forming. On the other hand experimentalists were able to show that the reaction was not proceeding through a concerted pathway by intercepting the intermediates involved. There remained, however, two ring systems methylenecyclopropanes and cyclobutenes—whose reactions with metal complexes seemed to be of a concerted nature. An analysis of the reactions of different metal complexes with these ring systems and the theoretical predictions provide a rationale for understanding these reactions.

Keywords. Metal orbital catalysis; methylenecyclopropanes; cyclobutenes; ring opening reactions; orbital symmetry; transition metal.

1. Introduction

Several organic molecules with severely strained ring systems owe their stability to symmetry constraints present in the reaction pathways available to them. These symmetry constraints essentially form the walls of a potential energy well in which the molecule is encaged. Ever since the presence of these energy barriers were expounded (Woodward and Hoffman 1971), there have been repeated attempts to find ways and means of overcoming these constraints. Although the use of photochemical energy has been successful in many cases, often it brings about undesirable results. Transition metal complexes have also been quite useful in bringing about certain transformations. It is the intent of this article to review the role played by orbital symmetry in the transition metal catalysed reactions involving methylenecyclopropanes and cyclobutenes and to present some of our recent results in this field.

2. Mechanisms of ring opening reactions

2.1 Theoretical models

As early as in 1965, the role of transition metal complexes in rendering accessible these formally forbidden reaction pathways, was analysed theoretically (Mango and Schachtschneider 1965). This treatment predicted that the symmetry constraints of most forbidden reactions would be removed if they occurred in the coordination sphere of the transition metal complex.

This theoretical treatment was followed by several others (Fukui and Inagaki 1975; Pearson 1976; Pettit *et al* 1969; Dewar 1971). In a very interesting article on the origin of

symmetry rules and their theoretical basis, Dewar (1971) has concluded that, just as antiaromatic molecules like cyclobutadiene are stabilized by transition metal complexes, anti-aromatic transition states will also be stabilized by transition metal complexes. This explanation completely ignores the role of supportive ligands and their symmetry. However, it has been shown (Mango and Schachtschneider 1971) that the presence of certain ligand geometries can result in a "restrictive ligand field" preventing the stabilization of the transition state.

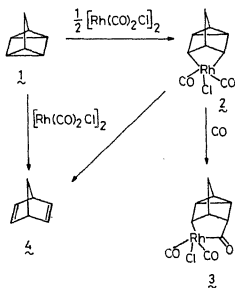
Another view of the mode of action was (Pettit *et al* 1969) that the symmetry requirements were not necessarily removed. However there was a drastic reduction in the energy barrier, since the transfer of electrons in the transition state now took place from the HOMO to the LUMO of the metal complex. These were invariably *d*-orbitals of the metal and hence the difference was much lower than the difference between the HOMO and LUMO of the free ligand. The difference in the *d*-orbital energies however depended on the ligands and their symmetry and hence this view readily accommodates the role of "restrictive ligand fields".

Although these theoretical treatments arrived at the general conclusion that the activation energy of forbidden concerted reactions would be lowered in the coordination sphere of a transition metal complex, proof that these reactions were indeed concerted had to come from experiments. Pathways involving metallacycles, metallocarbenes and zwitterionic intermediates had to be eliminated.

2.2 Preliminary experimental results

The conversion of quadricyclane to norbornadiene was catalyzed by Rh(1) complexes. This process a $\sigma_2S + \sigma_2S$ cycloreversion was thought to occur in the coordination sphere of rhodium and hence an example of metal orbital catalysis. However the detailed investigation of the mechanism (Cassar and Halpern 1971) showed that the reaction proceeded through distinct intermediates (figure 1) such as 2. These could be trapped in the presence of carbon monoxide to give 3, before it ring-opened to give norbornadiene.

The discovery of metallacycles as intermediates was followed by the discovery of



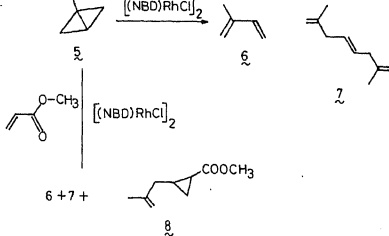
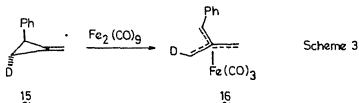
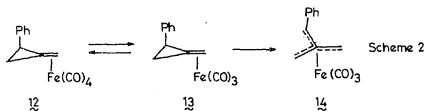
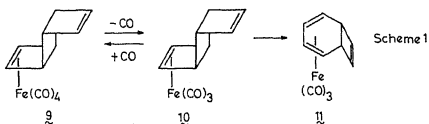


Figure 2. Carbene intermediates in metal-assisted ring opening of bicyclobutenes.



metallocarbenes (Gassman and Reitz 1973). An example of a ring opening reaction which was thought to proceed in a concerted fashion but is in reality a carbene-mediated process is shown in figure 2. The intermediate carbene could actually be trapped in the presence of a trapping agent.

In spite of these reactions which had disappointed theoretical chemists, interest in these fields continued unabated. Slegir *et al* (1974) reported the ring opening of an $\text{Fe}(\text{CO})_4$ complex of anti-tricyclo[4.2.0.0^{2,5}]octa-3-7-diene **9** to give an iron tricarbonyl complex **11**. The first step in the reaction sequence seemed to be a reversible dissociative step where the complex lost 'CO' to form a 16-electron complex **10**. This coordinatively unsaturated intermediate then ring opened to give **11** (scheme 1).

According to the Woodward and Hoffman rules, cyclobutenes can only ring open in a conrotatory fashion when thermally excited. However, if the fused ring cyclobutene in **9** opened in a conrotatory-allowed pathway it would end up with a trans double bond.

the energy of activation for this unfavourable process. In the absence of any evidence for metal stabilised reactive intermediates it was concluded that this was a concerted reaction occurring in the coordination sphere of the transition metal complex.

Another example of such a process came from the methylenecyclopropane ring system. Noyori *et al* (1969) reported the formation of a trimethylenemethane complex of $\text{Fe}(\text{CO})_3$ from phenylmethylenecyclopropane and $\text{Fe}_2(\text{CO})_9$ (scheme 2). Here, as in the reaction of cyclobutenes, a 16-electron intermediate seemed to have formed which then had ring-opened to give the final product. In this case, the ring opening of methylenecyclopropanes in the absence of the metal does not occur, since trimethylenemethane is an unstable biradical. However the mode of ring opening could be either disrotatory or conrotatory. The favoured mode of ring opening could be obtained from a theoretical calculation. In the interest of clarity it is best to examine the experimental results from these two ring systems separately.

3. Methylenecyclopropane ring opening reactions

The application of symmetry considerations to the ring opening of methylenecyclopropanes to give trimethylenemethane complexes was done by Pinhas and Carpenter (1980a). They distinguished three modes of ring opening, a disrotatory towards the metal pathway, a disrotatory away from the metal pathway, and a conrotatory pathway in which both components of the breaking bond turn in the same direction. Using extended Huckel calculations they found that the disrotatory away from the metal pathway was the most favourable pathway.

To check this prediction they also synthesized trans-2-phenylmethylenecyclopropane-3- d_1 4 and reacted it with $\text{Fe}_2(\text{CO})_9$. This yielded a single product 15 (Pinhas and Carpenter 1980b). If one made the reasonable assumption that the phenyl group was anti to the coordinated $\text{Fe}(\text{CO})_4$ in the initial complex, then the reaction had proceeded in the predicted mode (scheme 3). The stereospecificity with which the reaction had proceeded ruled out the intermediacy of a ring-opened zwitterionic species which had been implicated earlier (Billups *et al* 1972). It was also difficult to see how a metallacyclobutane intermediate could lead to a stereospecific product. Although this preliminary result was quite encouraging, the interaction of methylenecyclopropane with metal complexes is quite complex and leads to a variety of products depending on the metal and ligand. Even with the same metal and ligand system $\text{Fe}(\text{CO})_n$ one can obtain as many as four products depending on the substituent on the ring carbons (table 1).

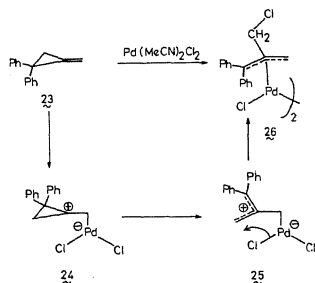
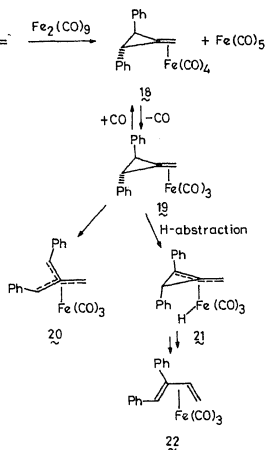
In the case of phenylmethylenecyclopropane itself two products were formed both stereospecifically (Pinhas 1980; Pinhas *et al* 1981). In view of this complexity, a more detailed study of the reaction was in order before making definitive claims about the mechanism (figure 3) of the reaction. The need for such a study was more obvious when two other research groups working on palladium and molybdenum came up with a cyclopropylation mechanism for explaining the stereospecificity in their reactions.

Methylenecyclopropanes can be cleaved by palladium complexes to yield a variety of complexes (Noyori and Takaya 1969; Green and Hughes 1976). However the cleavage of the 2-3 bond of the methylenecyclopropane was investigated by Hughes *et al* (1979).

Table 1. Relative percentages of different products isolated and characterised from the reaction of methylenecyclopropanes and $\text{Fe}_2(\text{CO})_9$.

Methylenecyclopropane	Intermediate			
	olefin- $\text{Fe}(\text{CO})_4$ complex*	Trimethylene- methane complex	Butadiene complex	Dinuclear complex
Methylenecyclopropane	—	—	100	—
2-Phenylmethylenecyclopropane	—	55	45	—
2,2-Diphenylmethylenecyclopropane	40	100	—	—
2,3-Trans-Dicarbomethoxy methylenecyclopropane	88	—	78	3
2,3-Cis-Dicarbomethoxy- methylenecyclopropane	65	—	88	1.5

* Percentage of intermediate with reference to starting material isolated at short reaction times.

**Figure 3.** Carpenter-Pinhas mechanism for the formation of butadiene and trimethylenemethane from 2,2-diphenylmethylenecyclopropane and iron carbonyl.**Figure 4.** Zwitterionic intermediates in $\text{Pd}(\text{II})$ -promoted ring opening of 2,2-diphenylmethylenecyclopropane.

Their results showed that the metal initially attacked the olefinic centre. The olefin complex then polarised to form a zwitterion with a cyclopropyl cation and an anionic metal centre. Cyclopropyl cations are known (Skell and Sandler 1958) to ring open very rapidly in a disrotatory fashion. Hence this zwitterion would undergo a ring opening

This mechanism seems to suggest that cleavage of the 2–3 bond of the methylenecyclopropane is the result of the positive charge on the central atom. Such a reaction sequence has been implicated in the formation of the cationic trimethylenemethane complex of $[Cp Mo(CO)]^+$ (Barnes and Green 1980). It is supposed that $[Cp Mo(CO)_3]^+$ coordinated to the olefin and formed a zwitterionic species. This subsequently underwent a disrotatory ring opening, which was followed by loss of carbon monoxide. The metal then slipped into place forming the trimethylenemethane complex.

Although the Carpenter–Pinhas mechanism accounts very well for the stereospecificity in the formation of the two products, trimethylenemethane and butadiene complexes, the formation of the trimethylenemethane complex could be equally well accounted for, by a zwitterionic mechanism. If this be the case the $Fe(CO)_4$ olefin complex partitions to give the zwitterionic intermediate and the $Fe(CO)_3$ complex. The $Fe(CO)_3$ complex would then be responsible for the formation of the butadiene complex but the zwitterion could ring open in a fast step and then lose a 'CO' to form the trimethylenemethane complex as shown in figure 5.

To distinguish between these two mechanisms, one had to prove that the 16-electron olefin complex was the intermediate which partitioned between the trimethylenemethane and butadiene complexes. Evidence suggesting that the 16-electron $Fe(CO)_3$ complex was indeed an intermediate in the pathway leading to the trimethylenemethane complex came when the olefin $Fe(CO)_4$ complex was isolated (Pinhas *et al* 1981) and characterised by x-ray crystallography. They then showed that careful treatment of this complex with trimethylamine-N-oxide a decarbonylating agent (Shvo and Hazum 1975) would lead to the formation of the trimethylenemethane complex. Another piece of evidence was that benzylidene acetone $Fe(CO)_3$ and " $Fe(CO)_3$ " transfer reagent (Scholes *et al* 1974; Graham *et al* 1977) brought about the conversion of phenylmethylenecyclopropane to the butadiene and trimethylenemethane complexes observed in its reaction with $Fe_2(CO)_9$. When stereospecifically labelled methylenecyclopropane was used in the reaction with $Fe(CO)_3$ transfer reagent it led to the same stereospecific products in the same ratio. This strongly suggested that the $Fe(CO)_3$ olefin complex was a common intermediate for the formation of the butadiene and trimethylenemethane complexes.

However the final and conclusive evidence came from the observation of an induced

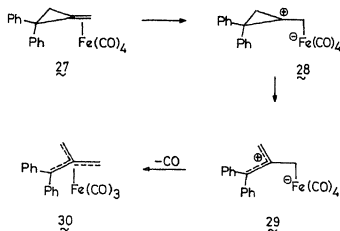


Figure 5. Zwitterionic mechanism applied to iron carbonyl-assisted ring opening of 2,2-

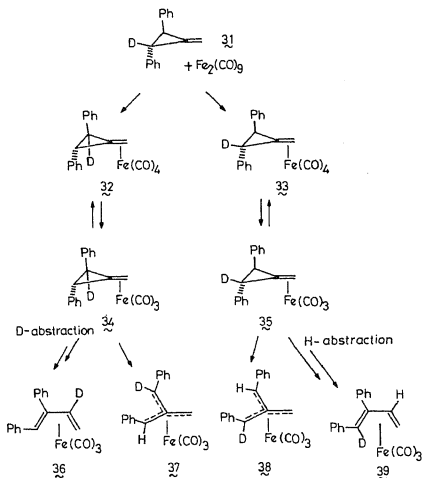


Figure 6. The induced kinetic isotope effect illustrated in the reaction of trans-2,3-diphenylmethylenecyclopropane-2-d₁ with Fe₂(CO)₉.

kinetic isotope effect (IKIE) (Samuelson and Carpenter 1981). This showed that the 16-electron olefin complex was partitioning between the butadiene and trimethylenemethane complexes as illustrated in figure 6. The IKIE arises from the fact that complexes 34 and 35 would be formed in equal proportions since they are identical except for the position of the isotope which is far removed from the reaction centre *i.e.* the olefin. However when 34 and 35 partition to give the butadiene and trimethylenemethane complexes, 34 gives more of the trimethylenemethane complex. This happens because D-abstraction is involved in the formation of the butadiene complex which makes the intermediate 34 to funnel into the easier pathway. However, there is no such favouring of one compound over the other in the reaction of 35. This leads to a ratio of 37/38 > 1.0. Since there was no direct isotope effect leading to this observation and since it was induced by an isotope effect in parallel pathway it has been termed the induced kinetic isotope effect.

If the cyclopropyl cation mechanism were operating, the difference in the ratio of 37/38 could not arise except as a result of a steric isotope effect as illustrated in figure 7. This effect is due to a difference in the C-H and C-D bond lengths and it would lead to a ratio of 37/38 > 1.0. The absence of steric isotope effect was confirmed by the reaction of 3-deuterio-2,2-diphenylmethylenecyclopropane. In this case there cannot be any induced kinetic isotope effect because the Fe(CO)₃ complex forms only the tri-

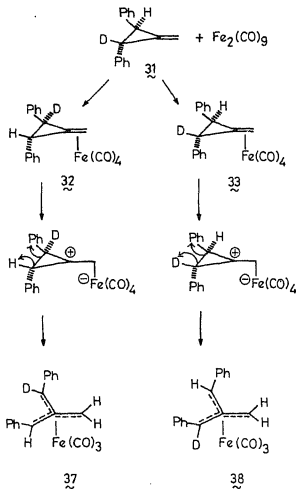


Figure 7. The steric isotope effect illustrated for the formation of trimethylenemethane complexes from *trans*-2,3-diphenylmethylene-2-*d*₁ and $\text{Fe}_2(\text{CO})_9$.

Thus the evidence strongly points to a metal orbital catalyzed reaction pathway for the formation of trimethylenemethane complexes from methylenecyclopropanes and ironcarbonyls.

4. Cyclobutene ring opening reactions

The initial results obtained by (Slegir *et al* 1974) showed that the iron carbonyls were capable of promoting a disrotatory ring opening of the cyclobutene. The extended Hückel calculation done by Pinhas and Carpenter (1980a) also indicated that the disrotatory mode of ring opening, where the breaking bond moved towards the metal, was the lowest energy pathway. The other disrotatory mode of ring opening where the breaking bond moved away from the metal, was the highest energy pathway with the conrotatory mode falling in between.

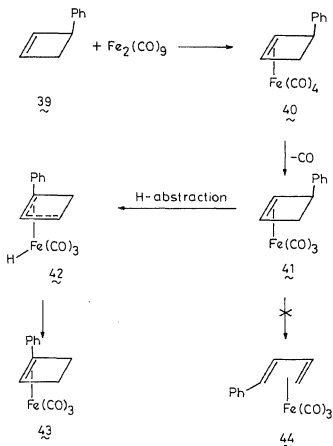
Although these calculations fell in line with the known results, the available experimental data was not a good test for theory. The parent cyclobutene does not ring open to give the butadiene complex with iron carbonyls. A possible reason for this might be inferred from the substituent effect observed in the ring opening reactions of methylenecyclopropanes. The absence of any substituent on C-2 and C-3 of the methylenecyclopropane leads to H-abstraction reaction only. When one phenyl group

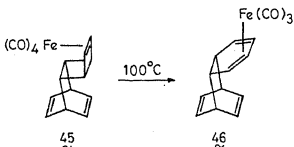
When two phenyl groups are present only the ring-opened product is formed. Thus there seems to be a bond weakening effect associated with the presence of phenyl groups. However this simple substituent effect is not borne out in the reactions of substituted cyclobutenes (Samuelson 1983). 3-Phenyl cyclobutene isomerises to 1-phenylcyclobutene on reaction with $\text{Fe}_2(\text{CO})_9$ possibly through a hydride intermediate as shown in figure 8. This seems to indicate that one is competing with a H-abstraction pathway.

One way to overcome this hurdle would be to lower the energy of activation for the ring opening reaction by increasing the number of substituents on the ring or suitably changing them. The other is to nullify the effect of H-abstraction by judicious substitution (Samuelson 1983). The latter approach has the added advantage that it is possible to judge the minimum substitution necessary to bring about the ring opening process. Both 3,3-diphenylcyclobutene and 1,3-diphenylcyclobutene failed to ring open on reaction with iron carbonyls. The former had the added advantage of a doubly weakened C-3-C-4 bond.

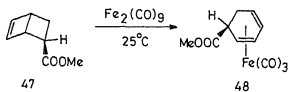
Thus simple cyclobutenes seem to be quite resistant to the ring opening reaction. This is quite surprising, considering the fact that bicyclobutenes ring open in such a facile reaction.

What is more disconcerting is that some bicyclic cyclobutenes ring open in a disrotatory—away from the metal mode. This pathway is predicted to be the highest energy pathway according to the calculations (Pinhas and Carpenter 1980a). One example is the ring opening of the $\text{Fe}(\text{CO})_4$ complex shown in scheme 4, to give the ring opened $\text{Fe}(\text{CO})_3$ complex of *O-p*-dibenzene (Grimme and Schneider 1977). The other





Scheme 4



Scheme 5

example is the ring opening of a bicyclic adduct formed from the reaction of cyclobutadiene and methyl acrylate with $\text{Fe}_2(\text{CO})_9$ (Samuelson 1983) as shown in scheme 5.

Apparently the iron coordinated *syn* to the carbomethoxy group as expected (Whitesides *et al* 1974). However contrary to the prediction made by theory the ring opened in a facile disrotatory—away from the metal mode!

In none of these reactions the presence of a metallacycle or other intermediates seems to be involved. Thus a metal orbital catalysed reaction seems to be the pathway chosen by the complex. However the predictions based on theory fall through.

5. Conclusion

Compared to the phenomenal success the Woodward and Hoffman rules have had in organic chemistry, the application of symmetry considerations to organotransition metal chemistry has yielded very little fruit. This is not to say that symmetry has no role in these reactions. What it does reveal is that the presence of the transition metal complex opens up a host of new pathways that were previously inaccessible to the free ligand.

This may involve a transition metal stabilised zwitterion, a metallacycle or a metallocarbene or even a metal orbital catalysed reaction pathway. For the simple reason that there are so many pathways available and at times not very different in energies—there does not seem to be a single factor determining the course of the reaction. The capability of the metal to form M–C bonds, C–C bond strength, steric encumbrances, and strain energy seem to play a role in determining the course of the reaction.

In the case of methylenecyclopropanes the choice of a metal in a higher oxidation state, as in the case of the molybdenum or the palladium complex, may lead to the formation of zwitterionic intermediates. The ability to form good M–C bonds could have also made this reaction pathway more favourable. The use of a first period transition metal in a low oxidation state favours the reaction proceeding through a metal orbital catalyzed pathway. The close correspondence between theory and experiment seems to indicate that symmetry plays a vital role in determining the mode

orbital symmetry-controlled pathway. It is possible that this reaction is proceeding through a distinct intermediate as in the case of the Rh(1) catalyzed reaction of quadricyclane. The other explanation is that the structure assigned to the diene $\text{Fe}(\text{CO})_3$ complexes in schemes 4 and 5 are incorrect. If the iron was coordinated on the other side of the diene unit in both cases, the ring opening has proceeded in complete accord with theory! An x-ray crystal structure determination of these complexes would resolve the question. Till now no such work has been done.

Further work has to be done in the cyclobutene ring system to determine the reaction mechanism. The predictions made by theory certainly had the effect of promoting research in this field and it will continue to do so till all questions regarding these reactions are solved satisfactorily.

Acknowledgements

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Structure and reactivity of palladium and platinum arylazooximates

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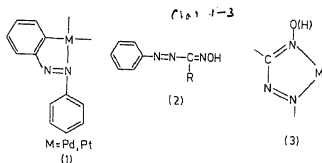
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Abstract. The structure and selected reactions of the title compounds are reviewed. Some highlights are as follows ($L =$ conjugate base of phenylazoacetaldoxime). While PtL_2 exist in *cis* and *trans* forms, PdL_2 occurs only in the *trans* form. In the crystalline state *cis*- PtL_2 consists of weakly held dimers ($Pt \cdots Pt$ 3.151 Å) but *trans*- PtL_2 consists of stacks of discrete molecules in the solid state. *Trans*- PdL_2 displays a surprisingly large tetrahedral distortion. The different metal-ligand bonds undergo selective cleavage by different reagents. Thus HCl and tertiary phosphines respectively cleave the M-N (oxime) and M-N (azo) bonds. Phosphine cleavage leads to interesting situations such as cone angle-dependent equilibria and fluxional behaviour. A rich redox chemistry consisting of successive reductions of the azo groups and of the metal are revealed electrochemically. *Cis*- PtL_2 unlike *trans*- PtL_2 undergoes a facile one-electron oxidation at low potentials. Another very curious reaction of *cis*- PtL_2 is the process in which an aromatic ring is thermally hydroxylated at the expense of an oximate oxygen atom. The meaning and significance of the observations are discussed.

Keywords. Palladium arylazooximates; platinum arylazooximates; selective bond cleavage; cone angles; fluxional behaviour; aromatic hydroxylation.

1. Introduction

The *ortho*-metallation of azobenzene (as in (1)) was discovered in the mid-sixties and the gate for many subsequent activities around this novel reaction became open (Cope and Sickman 1965; Omae 1979 and references therein). It is in this background that we initially examined whether the benzene ring would compete effectively with the oxime function when arylazooximes (2) (Kalia and Chakravorty 1970) are metallated with palladium and platinum. In practice binding was found to occur exclusively at azo- and oxime-nitrogens as in (3) (Kalia and Chakravorty 1969). The major features of the structure and reactivity of palladium and platinum arylazooximates are outlined in this article. All discussions are limited to the case $R=Me$ and the corresponding ligand phenylazoacetaldoxime is abbreviated as HL.



2. Parent species and their structures

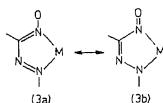
coordinated anion forming grossly planar MN_4 coordination spheres and five-membered chelate rings as in (3).

The *cis* and *trans* forms are furnished respectively by reacting HL with K_2PtCl_4 under acidic and basic conditions (Bandyopadhyay *et al* 1983a). The solvated proton is believed to have a role in favouring the *cis* form by a cooperative template effect of the metal and the proton whereby two oximate functions are brought together in a *cis* position *via* hydrogen bonding in the course of the chelative reaction.

The *cis*- PtL_2 molecules are arranged in an unexpected way in the crystalline state. The asymmetric unit consists of two crystallographically independent molecules which have almost identical internal dimensions and are close enough (Pt...Pt, 3.151 Å) to each other to constitute a loose dimer. The two coordination planes *i.e.* the mean planes of the four coordinated nitrogen atoms in the dimer are nearly parallel forming a dihedral angle of 16.4° . Each platinum atom is located slightly out of its coordination plane by a distance of ~ 0.1 Å. The directions of these displacements are such that the two platinum atoms approach each other (Bandyopadhyay *et al* 1983a). While Pt(II)-Pt(II) interaction in chelates is documented in literature (Hollis and Lippard 1983; Simonsen and Toftlund 1981) well characterized examples are not common.

In crystals of *trans*- PtL_2 the molecular arrangement is entirely different. Discrete molecules are stacked parallel to the *b* axis at intervals of 3.956 Å. Each molecule is centrosymmetric. The metal atom and the eight other atoms forming the two chelate rings define an excellent plane of C_{2h} symmetry. The deviation of each atom from the best plane is < 0.08 Å (Bandyopadhyay *et al* 1984).

Some selected average bond distance data are in table 1. These are consistent with the resonance (3a) $\leftrightarrow$ (3b). The free ligand structure is also known and it has pure azoimine ($-N=N-C=N-O$) character (Roy and Sengupta 1980).



2.2 *Trans*- PdL_2 : unprecedented tetrahedral distortion

Unlike PtL_2 , PdL_2 occurs in only one isomeric form (Bandyopadhyay *et al* 1981) now

Table 1. Selected average distances (Å)

Bond	<i>trans</i> - PdL_2	<i>trans</i> - PtL_2	<i>cis</i> - PtL_2
M-N(O)	2.027 (3)	2.015 (6)	1.954 (6)
M-N(Ph)	2.033 (3)	2.020 (6)	2.018 (7)
N-O	1.268 (4)	1.261 (8)	1.342 (19)
N(O)-C	1.339 (5)	1.348 (9)	1.322 (2)
(R)C-N	1.352 (5)	1.338 (9)	1.356 (6)
N=N	1.283 (4)	1.294 (9)	1.326 (5)

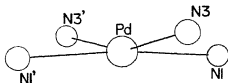


Figure 1. A view of the Pd coordination shell geometry in *trans*-PdL₂, showing the distortion from planarity towards tetrahedral geometry.

shown to be the *trans* form. However the crystals of *trans*-PtL₂ and *trans*-PdL₂ are not isomorphous. Discrete molecules are present in both cases but the molecular geometry and packing are dissimilar. There is no sort of stacking in *trans*-PdL₂ and the shortest Pd . . Pd distance is 6.636 Å (Bandyopadhyay *et al* 1984).

Each chelate ring is planar to within 0.06 Å. Even though the gross relative orientation of the two chelate rings is *trans*, the deviation of the PdN₄ coordination sphere from planarity towards the tetrahedral configuration is large (figure 1). The dihedral angle between the two planar chelate rings is 25.6°. The bond distances (and angles) within the chelate rings are similar in the palladium and platinum compounds (table 1).

The origin of the distortion in *trans*-PdL₂ and of the lack of it in *trans*-PtL₂ are unclear at present. Interplay of the following factors could be important: (i) stronger preference of platinum(II) for planar tetracoordination, (ii) gain in conjugation as the dihedral angle of the phenyl ring to the chelate ring decreases and (iii) increase in the steric repulsion between the phenyl ring and oxime oxygen of the adjacent ligand under conditions defined in (ii). The following observations are significant in this context: (i) the dihedral angle of the phenyl ring with the corresponding chelate ring is much smaller (24.8°) in *trans*-PdL₂ than in *trans*-PtL₂ (43.8°); (ii) in high boiling solvents PtL₂ undergoes (see below) an internal redox transformation in which an oximato oxygen atom migrates to the adjacent phenyl ring; and (iii) in tetrahedral Cu^I(HL)(L) the dihedral angle of the phenyl ring to the corresponding chelate ring is only ~ 1° (Dickman and Doedens 1980).

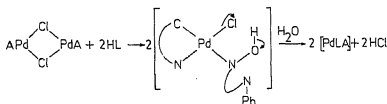
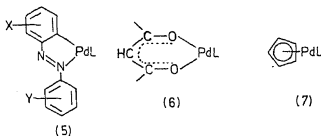
There have been several unsuccessful attempts in the past to utilize interligand steric crowding to introduce tetrahedral distortion in four coordinate *bis*-chelates of palladium(II). Good examples are certain salicylaldimines (Braun and Lingafelter 1967; Day *et al* 1968) and dipyrromethenes (March *et al* 1971). In both cases the metal coordination sphere retained planarity at the expense of intraligand bending. The tetrahedral distortion in *trans*-PdL₂ is unique and unprecedented for palladium(II).

2.3 Halo-bridged dimers

Addition of HL to PdCl₄²⁻ or Pd(NCPh)₂Cl₂ in aqueous ethanol affords the violet dimer (4) which is converted to green-coloured *trans*-PdL₂ on further addition of HL. The corresponding bromo species are similarly made and the platinum analogue of (4) is also known (Kalia and Chakravorty 1969; Mascharak and Chakravorty 1979a, 1980).

2.4 Mixed ligand species including organometallics

Violet complexes of type PdLA (5) are made by cleaving the halo-bridge in $\text{Pd}_2\text{Cl}_2\text{A}_2$ (A = *ortho*-metallated azobenzene as in (5) by HL. The reaction medium is a mixture of benzene and water. The latter acts as a base in the dehydrohalogenation reaction (scheme I). In effect the halo-bridge is split by the oxime-N atom of HL with subsequent elimination of HCl and chelate ring closure (Bandyopadhyay *et al* 1982).



Scheme 1.

The PdLA species occur as isomeric mixtures whose compositions are conveniently established with the help of ^1H NMR data. The isomerism originates from different modes of *ortho*-metallation with respect to X and Y and is carried over to PdLA from the precursor complex $\text{Pd}_2\text{Cl}_2\text{A}_2$. Substituent (X and Y) effects on isomer population are consistent with the electrophilic nature of the palladation reaction but the steric factor also plays an important role. A simple and accurate ^1H NMR method for isomer population analysis in the precursor complex $\text{Pd}_2\text{Cl}_2\text{A}_2$ has been based on bridge splitting and solubilisation by PPh_3 (Bandyopadhyay *et al* 1982).

Species of type (6) and (7) have also been synthesised but remains unreported so far (Bandyopadhyay and Chakravorty).

3. Selective cleavage of metal-ligand bonds

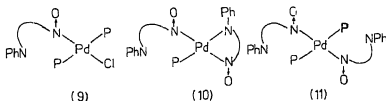
3.1 Bridge-splitting

A common reaction of halo-bridged species is the facile cleavage of the bridge by Lewis bases. The arylazooximates are no exceptions and adducts of type (8) are readily isolated by reacting (4) with amines(A) or tertiary phosphines(P) (Kalia and Chakravorty 1969; Mascharak *et al* 1977; Mascharak and Chakravorty 1979b, 1980).

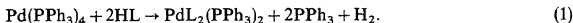


3.2 Pd-N (azo) cleavage

In the case of P further addition of base leads to selective cleavage of the chelate ring at the azo end leading to the formation of (9) which occurs in the solid state and displays interesting equilibria (see below) in solution. There are two major spectroscopic differences between (8) and (9). In (8) an allowed $d(\text{Pd}) \rightarrow \pi^*$ (chelated azoimine) transition occurs at $\sim 520 \text{ nm}$ ($\epsilon \sim 5000$); when the chelate ring is cleaved at the azo end (as in (9)) or at the oxime end (see below) this band disappears. The $^1\text{H NMR}$ $\delta(\text{Me})$ of L in (8) is $\sim 2 \text{ ppm}$ while in (9) it is 0.87 ppm due to the location of the methyl group well into the shielding cone of P (Mascharak and Chakravorty 1980).

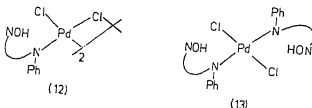


Tertiary phosphines also cleave the azo end of one or both rings in *trans*- PdL_2 affording (10) or (11), the latter being stable only in the solid state going over of (10) + P in solution. An alternative route to (11) is the oxidative addition of HL to $\text{Pd}(\text{PPh}_3)_4$ (Bandyopadhyay *et al* 1981)



3.3 Pd-N(oxime) cleavage

Selective cleavage of the oxime end is brought about by hydrogen chloride. The neutral oxime function is a weaker donor than the oximato anion (Chakravorty 1974). Hydrogen chloride first protonates the oximato function and the resultant chloride ion then displaces the Pd-N(oxime) bond. Thus from (4) red crystals of (12) arise. Interestingly the same product is furnished by hydrohalogenation of *trans* PdL_2 . Here displacement of the Pd-N(oxime) bond by chloride ion with the formation of the postulated intermediate (13) is followed by partial ligand elimination and dimerisation. Crystals of (12) readily lose hydrogen chloride to regenerate (4) in the presence of bases including moisture (Mascharak and Chakravorty 1980; Bandyopadhyay *et al* 1981).



By the successive application of HCl and P in any order the chelate ring gets cleaved at both ends leading to ligand elimination and formation of PdCl_2P_2 .

3.4 Case of platinum

Whereas cleavage reactions of platinum arylazooximates have not been studied as thoroughly as those of palladium analogues, the known reactions (Mascharak and Chakravorty 1980) are essentially analogous. A point of special interest is the isolation

Table 2. Cone angle (θ , degree) and equilibrium constant (K , mole⁻¹ lit) at 298 K

Phosphine	θ	$10^{-2} K$
PMe ₂ Ph	122	2310 ± 50
PMePh ₂	136	670 ± 20
PPh ₃	145	28 ± 2
P(<i>p</i> -tolyl) ₃	145	70 ± 2
P(cyclohexyl) ₃	170	0.5*
P(<i>o</i> -tolyl) ₃	194	0.006*

* Estimated value.

of the platinum analogue of postulated intermediate (13) in pure form. This strengthens the proposed mechanism for the conversion of *trans*-PdL₂ to (4) under hydrohalogenation in the presence of moisture.

3.5 Reversible binding of phosphines: cone angle correlations

We return to reconsider the species (8) and (9). The various phosphines(P) of interest are in table 2. When P is added to a solution of (8) in eg benzene, the 520 nm band progressively loses intensity. Variable concentration spectra display a well-defined isosbestic point. All results are in agreement with the presence of the equilibrium (2).



Equilibrium constant data obtained from spectral intensity data are in table 2.

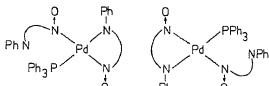
The observed trend in K values has been rationalised (Bandyopadhyay *et al* 1980). A measure of the steric demand of P is its cone angle (Tolman 1977). In case of predominant steric control of a reaction of the general type (3) the equilibrium constant usually decreases with increase in cone angle (θ) of P.



We considered the possibility that there may be an approximate linear correlation of free energy change or simply $\ln K$ with θ . Analysis of literature data indeed showed this to be true. The K data (table 2) of equilibrium (2) follows the linear $\ln K$ - θ relationship very well. The trend of this equilibrium with these phosphines is therefore set by phosphine bulk. Tricyclohexyl and tri-*o*-tolyl phosphines are too bulky to react ($K \sim 0$, table 2).

3.6 Phosphine binding and fluxional behaviour

This pertains to complexes of type (10) and we shall consider specifically the case of PdL₂(PPh₃) (Bandyopadhyay *et al* 1981). The $\delta(\text{Me})$ value (¹H NMR in CDCl₃) for



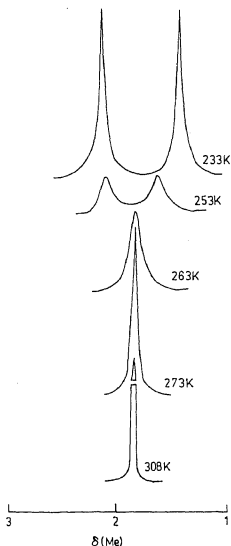


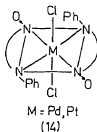
Figure 2. Temperature dependence of the ^1H methyl NMR signals of $\text{PdL}_2(\text{PPh}_3)$ in CDCl_3 ; recording amplitudes varies from temperature to temperature.

trans-PdL_2 is 2.13 ppm. At room temperature $\text{PdL}_2(\text{PPh}_3)$ also has a single sharp Me signal but with $\delta = 1.82$ ppm. Rapid scrambling of the chelated and unidentate ligands (a fast interconversion of (10a) and (10b) is implicated. On cooling below 293 K, the Me signal broadens progressively and around 253 K splitting into two signals occurs (figure 2). These sharpen on further cooling and finally at 233 K two well-defined sharp signals of equal intensity remain (δ 2.16 and 1.44 ppm) confirming that the instantaneous structure is indeed (10). The signal at higher field is assigned to unidentate L since here ligand flexibility can bring the methyl group within the shielding cone of the phosphine.

A probable mechanism for the fluxional behaviour is intramolecular nucleophilic attack (S_Ni) by the pendant azo-group resulting in displacement of the bound azo function. While the S_Ni path is documented in the displacement of phosphine by a free azo group (Cross and Tennent 1974), process (4) is unique in that both the forward and the backward reactions must have identical S_Ni dynamics since the attacking and leaving groups are identical.

Redox reactions

1 Oxidative addition of dihalogen: platinum(IV) and palladium(IV)



which has $^1\text{H } \delta_{\text{Me}}$ of 2.33 ppm. The halide ligands are *trans* (single ν_{PtCl} 324 cm^{-1}) and the vibration spectrum is more akin to that *trans*- PtL_2 than to *cis*- PtL_2 . The likely structure of PtL_2Cl_2 is (14). A *cis* $\rightarrow$ *trans* rearrangement of the PtL_2 moiety, therefore, occurs when Cl_2 reacts with *cis*- PtL_2 (Bandyopadhyay *et al* 1983a).

Green solutions of *trans*- PdL_2 in benzene on treatment with one equivalent of X_2 ($\text{X} = \text{Cl}, \text{Br}$) change colour to deep red. In the red solution diamagnetic species with δ_{Me} 2.33 ($\text{X} = \text{Cl}$) or 2.40 ($\text{X} = \text{Br}$) are present. It has not been possible to isolate such species—believed to be palladium(IV) species of type (14)—in the solid state because of their relative unstability which is not unexpected (Mursinik and Pross 1978). Ethanol reduces the red solution affording $\text{Pd}_2\text{Cl}_2\text{L}_2$ (4) in good yield (Bandyopadhyay *et al* 1981).

4.2 Reductive electrochemical reactions

In general the arylazooximates display voltammetric responses corresponding to reductions of ligand and metal. The situation is illustrated (figure 3) with the case PdLA (5, $\text{X} = \text{Y} = \text{H}$). The complex displays three reversible to quasireversible cyclic

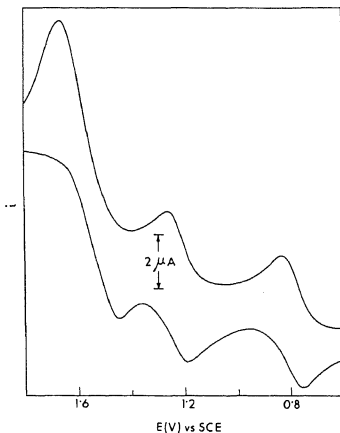


Figure 3. Cyclic voltammogram of PdLA in acetonitrile (0.1 M tetraethylammonium

oltammetric responses in acetonitrile solution corresponding to formal potentials of -0.76 , -1.19 and -1.46 V vs saturated calomel electrode (Bandyopadhyay *et al* 1982).

At -0.76 and -1.19 V the processes are respectively (4) and (5) corresponding to ligand reduction primarily at the azo functions.



It is known that the azo group can undergo the following successive one-electron reductions, equation (6), in aprotic solvents (Loufty and Sharp 1977). On the basis of our unpublished electrochemical studies on species of type PdLD and PdAD where D is an electroinactive bidentate ligand we have concluded that L is reduced more readily



than A. The two one-electron reductions in PdLA are therefore due to addition of one electron to the azo group of L (couple (4)) and one electron to that of A (couple (5)). At potentials more negative of couple (5) one more electron could in principle be added to each of the two $-\text{N}^{\cdot -}-\text{N}^{\cdot -}-$ groups. However, metal reduction intervenes before this level of reduction is achieved.

In the case of the couple at -1.46 V, the cathodic peak height corresponds to the transfer of two electrons. The anodic peak is smaller than the cathodic peak. These are good reasons to believe that processes (7) and (8) are involved. The direct conversion of



Pd^{II} to Pd⁰ is documented in phosphine complexes in aprotic media (Martelli *et al* 1974). There is no evidence that the Pd^I intermediate is formed.

3 The curious behaviour of *cis*-PtL₂

trans-PtL₂ shows successive azo reductions at -0.39 and -1.77 V. The corresponding reductions in *cis*-PtL₂ are at -0.27 and -1.76 V respectively. In addition the *cis* isomer shows a reversible one-electron oxidative response at $+0.43$ V. The *trans* isomer does not show this response (Bandyopadhyay *et al* 1983a).

The oxidation of *cis*-PtL₂ is believed to be due to the process (9)



in which the metal is oxidised. A plausible, though speculative, explanation for the relative ease with which the *cis* isomer (but not the *trans* isomer) can be oxidised is that delocalisation can occur over the *cis*-nitroxide system (15). No analogous possibility exists for the *trans* isomer.

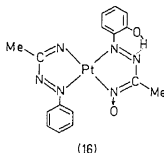


EPR spectrum is axial ($g_{\parallel}$ 1.946, $g_{\perp}$ 1.988; powder 77 K) with the expected ^{195}Pt hyperfine structure. Since $g_{\perp} > g_{\parallel}$ the paramagnetic species could have a d^7 configuration, could be PtL_2^+ itself (Bandyopadhyay *et al* 1983a).

4.4 A novel case of aromatic hydroxylation

When a suspension of *cis*- PtL_2 is boiled in xylene for a few hours a deep blue solution results from which blue crystals are obtainable. The deep blue colour is due to intense absorption in the red (635 nm; $\epsilon = 22500$).

The elemental composition of the blue complex is the same as that of PtL_2 . Proton NMR in CD_2Cl_2 shows the presence of two equally intense methyl signals (2.50 and 2.54 ppm) and a phenolic OH signal (11.00 ppm) apart from highly structured aromatic resonances (6.9–7.8 ppm). The complex true to its phenolic nature dissolves in aqueous alkali giving a deep blue solution. The blue complex has been examined x-ray crystallographically. Unfortunately there is the complication of crystallographic disorder. It is however clear that the crystal consists of monomolecular molecules of type (16) (Bandyopadhyay *et al* 1983b).



The central platinum atom resides on a site of mm symmetry and the ligands are disordered. The five-membered chelate ring and the platinum coordination sphere are planar. The $\text{O(H)} \cdots \text{NNPt}$ distance of 2.60(3) Å is indicative of hydrogen bonding which is also reflected in the broadness of the OH NMR signal.

In the reaction $\text{cis-PtL}_2 \rightarrow (16)$ an oximate oxygen may have been utilised to hydroxylate an adjacent aromatic ring, although convincing proof of an intramolecular redox transformation is lacking at present. In any case the observed reaction is of an unprecedented type.

Lastly, the blue colour of the medicinally relevant 'platinum blues' are usually associated with a polynuclear mixed valence core (Lippard 1982). The present work as well as other recent work (Overbosch *et al* 1982) show that a deep blue colour in platinum complexes can arise for different reasons in different cases. In the case of (16) the blue colour is no doubt due to charge transfer transitions involving both ligand and metal orbitals.

5. Concluding remarks

The arylazooximates under review display an impressive array of structure and reactivity patterns some of which are quite unusual. The phenomenon of aromatic hydroxylation is probably the most exciting development. The scope and mechanism

this fascinating reaction is being closely investigated. We have no answer as yet to questions such as 'does such a reaction occur in PdL₂ also?', 'does aereal oxygen play a role?' etc.

We conclude by noting that arylazooximates of a number of transition metals other than palladium and platinum have also been studied in our laboratories and a very brief summary appeared recently (Bandyopadhyay *et al* 1983a). Metal arylazooximates invariably have something interesting to display.

Acknowledgements

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Binuclear and polynuclear complexes of rhodium with nitrogen heterocycles as bridging ligands

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Abstract. A number of binuclear and polynuclear complexes of rhodium(I) with bridging nitrogen heterocycles are known. X-ray crystal structure analysis of some of the complexes has established the bridging nature of the heterocycles. The proximity of the metal atoms is found to considerably influence the electronic spectra of the complexes. Oxidative addition reactions of these compounds are yet to be properly investigated. Some of these compounds are efficient hydrogenation and hydroformylation catalysts.

Keywords. Binuclear complexes; polynuclear complexes; rhodium; nitrogen heterocycles; bridging ligands.

Introduction

Binuclear and polynuclear complexes of transition metals have received considerable attention because of the interesting electrical, optical and catalytic properties that could be associated with such systems. Several nitrogen heterocycles have been conveniently employed as bridging ligands in the isolation of such complexes (Coleman *et al* 1982; Manza 1983; Newkome *et al* 1982; Powers and Meyer 1978; Stobart *et al* 1980; Uson *et al* 1982a). The heterocycles used in this way are bidentate or tetradentate species with the coordinating nitrogen atoms located at positions convenient for bridge formation. They are essentially five- and six-membered rings or their extended forms or their derivatives. While heterocycles derived from six-membered rings and containing two or four nitrogen donor sites can directly bridge two metal centres, those derived from five-membered rings act as bridging ligands in their anionic forms. The heterocycles that have been successfully employed as bridging ligands are depicted in figures 1 and 2. This review is confined to binuclear and polynuclear complexes of rhodium containing the aforesaid bridging heterocycles. Most of these complexes have the metal atom in the oxidation state + 1.

General methods of synthesis

The dihalobridged binuclear complexes of the type $L_2Rh(\mu-X_2)RhL_2$ (X = halogen; L_2 = diolefin, $(CO)_2$) are convenient starting materials (Abel *et al* 1959; Chatt and Manzenz 1957; Deeming and Sharratt 1975; Roe and Massey 1971) for the isolation of a majority of rhodium(I) complexes with bidentate or tetradentate bridging hetero-

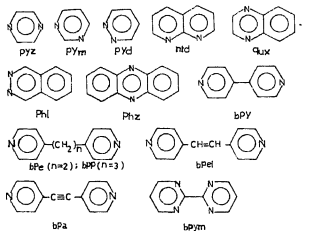


Figure 1. Heterocycles derived from six-membered rings.

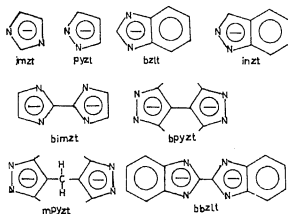
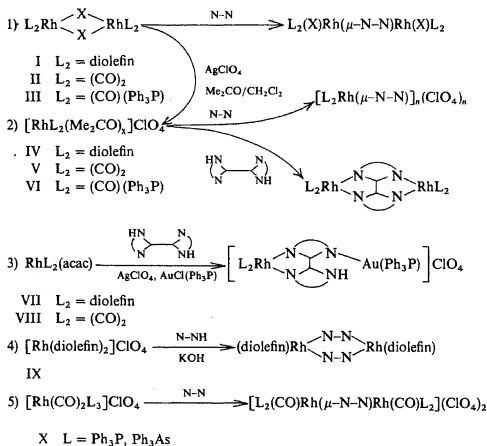


Figure 2. Heterocycles derived from five-membered rings.

cycles*. A few cationic complexes of rhodium(I) also serve as precursors in several reactions. Methods of isolating rhodium(I) complexes with bridging nitrogen heterocycles are summarised below.



*The term "bidentate" generally means "chelate" (*i.e.* endobidentate) and hence a bidentate ligand (N-N or N-NH) which cannot form a chelate but bonds to two metal atoms is termed as an "exobidentate" (Trofimenko 1972). Similarly a tetradentate ligand  which bonds to two metal atoms may be referred to as an "endo-exotetradentate".

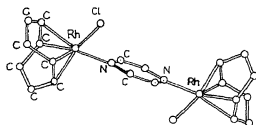
3. Complexes containing pyrazine, phenazine and quinoxaline

Pyz and phz react with complex I in acetone to give complexes of the formula (diolefin)-(X)Rh(μ -N-N)Rh(X)(diolefin) (diolefin = cod, nbd; N-N = pyz, phz) (Halesha *et al* 1983; Siedle *et al* 1983). In the cod complexes pyz can be replaced by the more bulkier ligands like phz. Endobidentate ligands such as bipy and phen, however, cleave the pyz bridge in cod containing compounds to form mononuclear ionic complexes. In benzene, the binuclear complexes undergo substitution of the diolefin with carbon monoxide to give $(\text{CO})_2(\text{X})\text{Rh}(\mu\text{-N-N})\text{Rh}(\text{X})(\text{CO})_2$. The latter complexes can also be isolated by treating complex II in benzene with the bridging heterocycles (Balch and Cooper 1979; Halesha *et al* 1983; Siedle *et al* 1983). The pyz bridged bromo carbonyl is, however, very unstable. Qux behaves similar to the above mentioned heterocycles in its reaction with complex I (X = Br; diolefin = cod). However the compound is not as stable as its pyz or phz analogs probably due to the less symmetric nature of the bridging heterocycle. Carbonyls of the type $(\text{CO})_2(\text{X})\text{Rh}(\mu\text{-qux})\text{Rh}(\text{X})(\text{CO})_2$ are made by reacting complexes II with qux. The stability of the carbonyl complexes follows roughly the order $\text{pyz} < \text{qux} < \text{phz}$ (Halesha and Reddy, Unpublished results). IR and PMR data of some of these complexes are listed in table 1.

X-ray crystal structure analysis of $(\text{cod})(\text{Cl})\text{Rh}(\mu\text{-pyz})\text{Rh}(\text{Cl})(\text{cod})$ has unequivocally established the dinuclear nature of the complex with the two metal atoms bridged *via* the pyz nitrogens (Rh-N = 2.1 Å). The pyz ring is virtually planar and makes an angle of 56.9° to the coordination plane of the metal atoms due to steric effects arising from bulky chlorine atoms which are located *trans* to each other (figure 3; Halesha *et al* 1983).

Table 1. IR and PMR spectral data of pyz, phz and qux complexes.

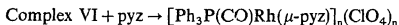
Complex	PMR data (δ)/ ν_{CO} (cm^{-1})
$(\text{cod})\text{ClRh}(\mu\text{-pyz})\text{RhCl}(\text{cod})$	1.80, 2.49, 4.21 (cod); 8.67 (pyz)
$(\text{OC})_2\text{ClRh}(\mu\text{-pyz})\text{RhCl}(\text{CO})_2$	8.82 (pyz)/2015, 2105
$(\text{cod})\text{BrRh}(\mu\text{-pyz})\text{RhBr}(\text{cod})$	1.80, 2.49, 4.21 (cod); 8.69 (pyz)
$(\text{OC})_2\text{BrRh}(\mu\text{-pyz})\text{RhBr}(\text{CO})_2$	—/2016, 2095
$(\text{OC})_2\text{ClRh}(\mu\text{-phz})\text{RhCl}(\text{CO})_2$	8.12, 9.43 (phz)/2005, 2085
$(\text{OC})_2\text{BrRh}(\mu\text{-phz})\text{RhBr}(\text{CO})_2$	—/2005, 2085
$(\text{OC})_2\text{ClRh}(\mu\text{-qux})\text{RhCl}(\text{CO})_2$	—/2005, 2090
$(\text{OC})_2\text{BrRh}(\mu\text{-qux})\text{RhBr}(\text{CO})_2$	—/2010, 2080
$[(\text{OC})_2\text{ClRh}(\mu\text{-pyz})\text{RhCl}(\text{CO})_2]_{4.2}$	—/2015, 2105
$[(\text{OC})\text{Rh}(\mu\text{-pyz})\text{Rh}(\text{CO})]_n(\text{ClO}_4)_{2n}$	—/2050, 2120
$[(\text{OC})\text{Ph}_3\text{PRh}(\mu\text{-pyz})]_n(\text{ClO}_4)_n$	—/2010



The qux and phz complexes may be expected to show more tilting of the bridging ligand with respect to the coordination plane. In fact molecular model studies for the monomeric complex $\text{RhCl}(\text{cod})\text{phz}$ indicate that non-bonded repulsions between the phz peri-hydrogen atoms and the halogen and cod groups cause the heterocycle to twist so that its molecular plane is perpendicular to the rhodium plane (Siedle *et al* 1983). A similar orientation of phz molecule may be expected in the binuclear complex $(\text{cod})\text{ClRh}(\mu\text{-phz})\text{RhCl}(\text{cod})$. In this orientation the phz π^* and *trans* olefin π^* orbitals do not overlap with and compete for electron density from the same filled metal 4d orbital. This sterically enforced twisting of the phz ligand would lead to strong metal-nitrogen bonds. The dinuclear complexes (containing cod and pyz or phz) are good hydrogenation catalysts for the conversion of alkenes to alkanes, and nitro compounds to amino compounds (Leelamani *et al*, Unpublished results).

For the carbonyl complex $(\text{CO})_2\text{ClRh}(\mu\text{-pyz})\text{RhCl}(\text{CO})_2$, on the basis of molecular models, it is suggested that the two $\text{Rh}(\text{CO})_2\text{Cl}$ planes can be coplanar with the pyz ligand. The molecule is thus expected to be flat and may be able to stack in such a way that one rhodium(I) site lies over another. In the uv-visible region, the complex shows absorption bands at 300, 375, 415 and 650 nm, and the spectrum, with the exception of the longest wavelength band, is analogous to that of the phz isolog. However the longest wavelength band is suggested to be similar to that found for rhodium(I) complexes wherein the metal atoms are held in close proximity by bridging isocyanides (Mann *et al* 1980). Attempts to oxidise the above carbonyl with iodine have produced a black compound of the composition $[(\text{CO})_2\text{ClRh}(\mu\text{-pyz})\text{RhCl}(\text{CO})_2]_n\text{I}_{4.2}$ in which the metal ion continues to remain in the +1 oxidation state *vide infra* (table 1). It is likely that the iodo compound is a partially oxidised derivative of the parent compound (Siedle *et al* 1983). In the carbonyls of the formula $(\text{CO})_2\text{XRh}(\mu\text{-phz})\text{RhX}(\text{CO})_2$ the heterocyclic ring may be expected to be positioned perpendicular to the $\text{Rh}(\text{CO})_2\text{X}$ planes so that there is little opportunity for intermolecular interaction.

Reaction of complex IV (diolefin = cod, nbd, tfb) with pyz gives polynuclear cationic species $[(\text{diolefin})\text{Rh}(\text{pyz})]_n(\text{ClO}_4)_n$ containing bridging pyz. The diolefin in these complexes may be completely replaced by carbon monoxide to yield the carbonyl complex $[(\text{CO})_2\text{Rh}(\mu\text{-pyz})]_n(\text{ClO}_4)_n$. This carbonyl may also be obtained by employing the chloro carbonyl dimer (II) as the precursor and the reaction proceeds *via* the formation of complex V. The above carbonyl reacts with Ph_3P , in stoichiometric quantities to produce the mononuclear complex $[\text{Rh}(\text{CO})\text{pyz}(\text{Ph}_3\text{P})_2]\text{ClO}_4$. The polynuclear complex $[\text{Ph}_3\text{P}(\text{CO})\text{Rh}(\mu\text{-pyz})]_n(\text{ClO}_4)_n$ has, however, been made by the following reaction (Uson *et al* 1981b).



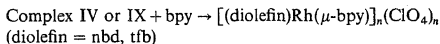
Yeh *et al* (1979) have prepared a mixed metal binuclear complex $(\text{NH}_3)_5\text{Rh}(\mu\text{-pyz})\text{Fe}(\text{CN})_5$ by treating $\text{Na}_3[\text{Fe}(\text{CN})_5\text{NH}_3] \cdot 3\text{H}_2\text{O}$ with $[\text{Rh}(\text{NH}_3)_5(\text{pyz})]^{3+}$ under argon. In the electronic spectrum of the complex an absorption band at 570 nm is observed and this is assigned to metal-to-ligand charge-transfer transition. The metal ions in the complex have well-defined oxidation states, *i.e.* Rh(III)-Fe(II), in contrast to trapped valences in the corresponding Ru-Fe complex, *i.e.*, Ru(III)-Fe(II) or Ru(II)-Fe(III), or a delocalised situation.

4. Complexes containing 4,4'-bipyridyl, 1,2-bis(4-pyridyl)ethane and related heterocycles

Mononuclear five-coordinate cationic complexes of the formula $[\text{Rh}(\text{CO})_2\text{L}_3]\text{ClO}_4$ ($\text{L} = \text{Ph}_3\text{P}$, Ph_3As) react with bpy in ethanol to yield binuclear heterocycle bridged complexes of the type $[\text{L}_2(\text{CO})\text{Rh}(\mu\text{-bpy})\text{Rh}(\text{CO})\text{L}_2](\text{ClO}_4)_2$ where the metal ion has coordination number four. Under similar conditions with pyz, only mononuclear complexes of the formula $[\text{Rh}(\text{CO})\text{L}_2(\text{pyz})]\text{ClO}_4$ are obtained. While the bpy complexes are 1:2 electrolytes in nitrobenzene, the pyz complexes are 1:1 electrolytes (Reddy and Ramesh 1975).

The exobidentate nitrogen heterocycles, bpy, bpe and bpel react with complex I in acetone to produce yellow products of the composition $(\text{cod})\text{XRh}(\mu\text{-N-N})\text{RhX}(\text{cod})$ ($\text{N-N} = \text{bpy}$, bpe , bpel). The bpy complex ($\text{X} = \text{Cl}$) is found to be a good catalyst for the hydrogenation of 1-heptene to heptane and some organic nitro compounds to amino compounds (Leelamani *et al*, Unpublished results). It is observed that the bpy complexes, on treatment with endobidentate ligands bpy and phen, undergo bridge cleavage reaction to yield mononuclear ionic complexes. The cod groups in the parent binuclear complexes can be replaced by CO. The carbonyl $(\text{CO})_2\text{ClRh}(\mu\text{-bpy})\text{RhCl}(\text{CO})_2$ may also be obtained by the reaction of bpy either with complex II ($\text{X} = \text{Cl}$) in benzene or carbonylated alcoholic solution of rhodium trichloride (Halesha *et al* 1983; Halesha and Reddy, Unpublished results). The ligand bpp, which may be considered as similar to bpy, reacts with complex II ($\text{X} = \text{Cl}$) to give yellow binuclear complex $(\text{CO})_2\text{ClRh}(\mu\text{-bpp})\text{RhCl}(\text{CO})_2$ which shows an absorption band at 343 nm in acetone (Balch and Cooper 1979). IR data of the above complexes (table 2) suggest *cis* positions for the carbonyl groups in the square planar geometry around the metal ion.

Polynuclear complexes with bridging bpy are formed according to the following reaction. The diolefins in these complexes undergo



substitution with carbon monoxide in dichloromethane to afford the polynuclear

Table 2. IR and PMR spectral data of bpy, bpe, bpp and bpel complexes.

Complex	PMR data (δ)/ ν_{CO} (cm^{-1})
$(\text{cod})\text{ClRh}(\mu\text{-bpy})\text{RhCl}(\text{cod})$	1.86, 2.52, 4.21 (cod); 7.46, 8.86 (bpy)
$(\text{cod})\text{BrRh}(\mu\text{-bpy})\text{RhBr}(\text{cod})$	1.83, 2.48, 4.25 (cod); 7.44, 8.86 (bpy)
$(\text{cod})\text{ClRh}(\mu\text{-bpe})\text{RhCl}(\text{cod})$	1.83, 2.50, 4.14 (cod); 2.90, 7.20, 8.62 (bpe)
$(\text{cod})\text{ClRh}(\mu\text{-bpel})\text{RhCl}(\text{cod})$	1.85, 2.49, 4.18 (cod); 7.22, 7.40, 8.66 (bpel)
$(\text{nbd})\text{ClRh}(\mu\text{-bpy})\text{RhCl}(\text{nbd})$	1.33, 3.87, 4.02 (nbd); 7.50, 8.59 (bpy)
$(\text{OC})_2\text{ClRh}(\mu\text{-bpy})\text{RhCl}(\text{CO})_2$	—/2000, 2090
$(\text{OC})_2\text{BrRh}(\mu\text{-bpy})\text{RhBr}(\text{CO})_2$	—/2020, 2080
$(\text{OC})_2\text{ClRh}(\mu\text{-bpp})\text{RhCl}(\text{CO})_2$	—/1997, 2091
$[(\text{OC})_2\text{Rh}(\mu\text{-bpy})]_n(\text{ClO}_4)_n$	—/2040, 2100
$[\text{Ph}_3\text{P}(\text{OC})\text{Rh}(\mu\text{-bpy})]_2(\text{ClO}_4)_2$	—/2000
$[\text{Ph}_3\text{As}(\text{OC})\text{Rh}(\mu\text{-bpy})]_2(\text{ClO}_4)_2$	—/1095

carbonyl complex $[(\text{CO})_2\text{Rh}(\mu\text{-bpy})]_n(\text{ClO}_4)_n$. One carbonyl group per metal atom in the latter compound may be replaced by Ph_3P with the retention of the polynuclear structure. Further addition of Ph_3P in stoichiometric quantities produces the binuclear complex $[(\text{Ph}_3\text{P})_2(\text{OC})\text{Rh}(\mu\text{-bpy})\text{Rh}(\text{CO})(\text{Ph}_3\text{P})_2](\text{ClO}_4)_2$ (Uson *et al* 1981b; Reddy and Ramesh 1975).

A mixed metal binuclear complex $(\text{NH}_3)_5\text{Rh}(\mu\text{-bpy})\text{Fe}(\text{CN})_5$ has been obtained by reacting $[\text{Rh}(\text{NH}_3)_5(\text{bpy})]^{3+}$ with $[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]^{3-}$. The complex shows an absorption band at 515 nm due to metal-to-ligand charge-transfer transition. As in the pyz analog, the metal ions in the complex possess well-defined oxidation states (Yeh *et al* 1979).

5. Complexes containing 1,8-naphthyridine

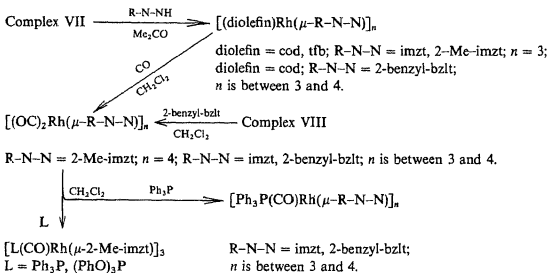
Reaction of complex II ($\text{X} = \text{Cl}$) with ntd in benzene produces green needles of the binuclear species $(\text{CO})_2\text{ClRh}(\mu\text{-ntd})\text{RhCl}(\text{CO})_2$ (figure 4a). In the electronic spectrum of the complex, the longest wavelength band located at 422 nm has been assigned to metal-to-ligand spin allowed ($d_{z^2} \rightarrow \pi^*$) transition. The corresponding absorption band in the mononuclear complex $\text{Rh}(\text{CO})_2\text{Cl}(\text{ntd})$ is found at 335 nm. The shifting of the $d_{z^2} \rightarrow \pi^*$ band to longer wavelength (or lower energy) is attributed to the close proximity of the metal centres in the binuclear complex (Balch and Cooper 1979). Such an observation has also been made in several binuclear rhodium(I) complexes (Mann *et al* 1980).

Complex II ($\text{X} = \text{Cl}$) also reacts with $\text{Ir}(\text{CO})_2\text{Cl}(\text{ntd})$ in benzene to give deep blue crystals of the heterobinuclear species $(\text{CO})_2\text{ClRh}(\mu\text{-ntd})\text{IrCl}(\text{CO})_2$ (figure 4b). For this complex, the $d_{z^2} \rightarrow \pi^*$ band occurs at 465 nm.

6. Complexes containing imidazolate, benzimidazolate and their derivatives

Noriaki *et al* (1977) have synthesised trinuclear rhodium complexes of the type $[\text{L}_2\text{Rh}(\mu\text{-N-N})]_3$ ($\text{L}_2 = \text{cod}$; $\text{N-N} = \text{imzt}$, bzlt ; $\text{L} = \text{C}_2\text{H}_4$; $\text{N-N} = \text{imzt}$) by treating $[\text{L}_2\text{Rh}(\mu\text{-Cl})]_2$ ($\text{L}_2 = \text{cod}$, $(\text{C}_2\text{H}_4)_2$) with butyl lithium/hexane and N-NH in thf. The imidazolate bridged trimer having cod is also obtained by reacting either complex VII with imztH in acetone or complex I with $\text{Au}(\text{imzt})(\text{Ph}_3\text{P})$ in dichloromethane (Uson *et al* 1981c). This complex is found to be an active hydroformylation catalyst for the conversion of olefins to aldehydes (Tanaka *et al* 1977). A number of other tri- and tetranuclear species containing the derivatives of imzt and bzlt have also been synthesised (Tiripicchio *et al* 1982; scheme 1). The trimeric and tetrameric nature of the above complexes has been proposed on the basis of molecular weight determinations in chloroform. The tetrameric structure for the compound $[(\text{OC})_2\text{Rh}(\mu\text{-2-Me-imzt})]_4$ has been confirmed by x-ray diffraction studies (figure 5; mean $\text{Rh-N} = 2.06 \text{ \AA}$).





Scheme 1

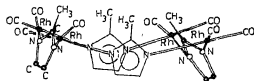
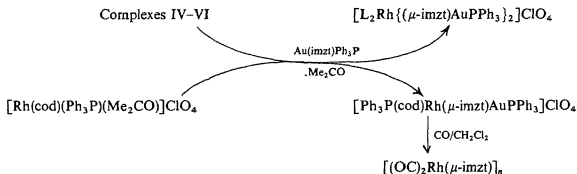


Figure 5. Structure of $[(\text{OC})_2\text{Rh}(\mu\text{-2-Me-imzt})]_4$.

Oro *et al* (1983) have obtained yellow cationic complexes of the type $(\text{diolefin})\text{Rh}(\mu\text{-bbzdH}_2)\text{Rh}(\text{diolefin})](\text{ClO}_4)_2$ (diolefin = cod, tfb) by the addition of the benzimidazole derived ligand bbzdH₂ either to complex IV in acetone or to complex IX in dichloromethane. On the other hand, bbzdH₂ reacts with complex I ($\text{R} = \text{Cl}$) in methanol to yield the neutral binuclear complex $(\text{diolefin})\text{ClRh}(\mu\text{-bbzdH}_2)\text{RhCl}(\text{diolefin})$. The tfb containing compound of the latter series in the presence of triethylamine in methanol, undergoes elimination of HCl to produce light yellow tetrameric complex of the composition $[(\text{tfb})\text{Rh}(\mu\text{-bbzd})\text{Rh}(\text{tfb})]_2$. Bubbling carbon monoxide through a solution of this complex in chloroform gives an impure polymeric complex $[(\text{OC})_2\text{Rh}(\mu\text{-bbzd})\text{Rh}(\text{CO})_2]_n$ which on addition of Ph_3P in stoichiometric quantities produces $[\text{Ph}_3\text{P}(\text{CO})\text{Rh}(\mu\text{-bbzd})\text{Rh}(\text{CO})\text{Ph}_3\text{P}]_n$. The parent tetrameric complex also reacts with $[\text{AuL}(\text{Me}_2\text{CO})_x](\text{ClO}_4)$ ($\text{L} = \text{Ph}_3\text{P}$) to yield $[(\text{tfb})\text{Rh}(\mu\text{-bbzd})\text{Rh}(\text{tfb})\text{Au}_2\text{L}_2]_n(\text{ClO}_4)_{2n}$ which with CO in chloroform undergoes displacement of tfb to afford the yellow complex $[(\text{OC})_2\text{Rh}(\mu\text{-bbzd})\text{Rh}(\text{CO})_2\text{Au}_2\text{L}_2]_n(\text{ClO}_4)_{2n}$. The last complex with L ($\text{Rh}/\text{L} = 1/1$) loses one CO group per metal atom to give $[\text{Ph}_3\text{P}(\text{CO})\text{Rh}(\mu\text{-bbzd})\text{Rh}(\text{CO})(\text{Ph}_3\text{P})\text{Au}_2\text{L}_2]_n(\text{ClO}_4)_{2n}$.

Uson *et al* (1981c) have reported that heteronuclear complexes with Rh-heterocycle- μ bridges are formed when complexes IV–VI and $[\text{Rh}(\text{cod})(\text{Ph}_3\text{P})(\text{Me}_2\text{CO})]\text{ClO}_4$ are reacted with $\text{Au}(\text{imzt})\text{Ph}_3\text{P}$ in acetone as illustrated below. Molecular weight measurements on the last polymeric carbonyl complex indicate that the value of n is between 3 and 4. Reaction of complex III with $\text{Pt}(\text{imzt})\text{dppe}$ in acetone produces heterotetranuclear complex $[(\text{cod})\text{Rh}(\mu\text{-imzt})_2\text{Pt}(\text{dppe})]_2(\text{ClO}_4)_2$ in which the cod groups can be substituted by carbon monoxide.



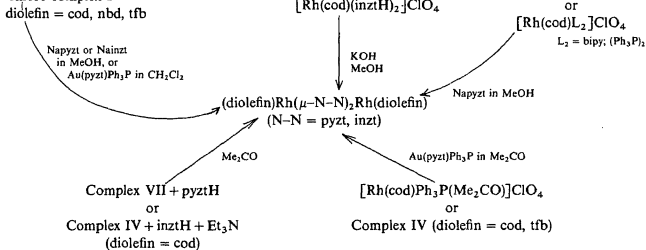
7. Complexes containing pyrazolate, indazolate and their derivatives

PyztH reacts with $[(\text{C}_2\text{H}_4)_2\text{Rh}(\mu\text{-Cl})]_2$ in methanol to give the red complex $(\text{C}_2\text{H}_4)_2\text{Rh}(\mu\text{-pyzt})_2\text{Rh}(\text{C}_2\text{H}_4)_2$ (Uson *et al* 1981a). Complexes of the formula $(\text{diolefin})\text{Rh}(\mu\text{-N-N})_2\text{Rh}(\text{diolefin})$ (N-N = pyzt, inzt) are obtained from several routes (Uson *et al* 1981a, 1982e) and some of these are visualised below (scheme 2).

The marked stability of the pyzt bridges in these complexes is reflected in their non-reactivity towards Ph_3P or $(\text{PhO})_3\text{P}$. The diolefin in some of these complexes can be displaced partially or completely by CO to get either $(\text{cod})\text{Rh}(\mu\text{-inzt})_2\text{Rh}(\text{CO})_2$ or $(\text{OC})_2\text{Rh}(\mu\text{-inzt})_2\text{Rh}(\text{CO})_2$ and the reactions are reversible. The diolefin containing carbonyl is also formed when $[\text{Rh}(\text{diolefin})(\text{inztH})]_2\text{ClO}_4$ (diolefin = cod, nbd, tfb) is reacted with either complex V or VIII in the presence of Et_3N . On the other hand, when the above cationic complex of inztH is treated with either $\text{Rh}(\text{CO})\text{Ph}_3\text{P}(\text{acac})$ or complex VI, in the presence of Et_3N , it yields $(\text{diolefin})\text{Rh}(\mu\text{-inzt})_2\text{Rh}(\text{CO})\text{Ph}_3\text{P}$ from which the diolefin can be displaced by CO. The carbonyl dimers (N-N = pyzt, inzt) are conveniently prepared by reacting complex II (X = Cl) with the heterocycles in the presence of Et_3N (Borkett and Bruce 1974; Uson *et al* 1982e).

Trofimenko (1971) is the earliest to report the synthesis of $\text{L}_2\text{Rh}(\mu\text{-3,5-Me}_2\text{pyzt})_2\text{RhL}_2$ ($\text{L}_2 = \text{cod}, (\text{CO})_2$) starting from complex I or II (X = Cl) and 3,5-Me₂-pyztH. According to molecular models the metallocycles are not planar but puckered in the boat form (Trofimenko 1972). Complex II also reacts with $\text{Au}(3,5\text{-Me}_2\text{-4-NO}_2\text{-pyzt})\text{Ph}_3\text{P}$ in benzene to give the corresponding heterocycle bridged rhodium carbonyl dimer (Minghetti *et al* 1979). Similar carbonyl dimers are probably formed when CO is bubbled through dichloromethane solutions of $(\text{diolefin})\text{Rh}(\mu\text{-pyzt})_2\text{Rh}(\text{diolefin})$ complexes since these on addition of a tertiary phosphine produce $\text{L}(\text{CO})\text{Rh}(\mu\text{-pyzt})_2\text{Rh}(\text{CO})\text{L}$ ($\text{L} = \text{Ph}_3\text{P}, p\text{-tolyl}_3\text{P}, (p\text{-ClC}_6\text{H}_4)_3\text{P}, (p\text{-OMeC}_6\text{H}_4)_3\text{P}, (\text{PhO})_3\text{P}$) (Uson *et al* 1981a). The Ph_3P complex can also be obtained by treating $\text{Rh}(\text{CO})\text{L}(\text{acac})$ with pyztH in $\text{Me}_2\text{CO-CH}_2\text{Cl}_2$. The inzt analog is also known (Uson *et al* 1982e). Such complexes have also been made by reacting $[(\text{OC})_2\text{Rh}(\mu\text{-R-pyzt})]_2$ ($\text{R} = 3,5\text{-Me}_2, 3,5\text{-Ph}_2$) with tertiary phosphite, phosphines or arsine (Powell *et al* 1982). The x-ray crystal structure of $(\text{PhO})_3\text{P}(\text{OC})\text{Rh}(\mu\text{-pyzt})_2\text{Rh}(\text{CO})\text{P}(\text{OPh})_3$ complex (figure 6; $\text{R} = \text{H}$; $\text{Q} = \text{CO}$; $\text{L} = (\text{PhO})_3\text{P}$) has been determined (Uson *et al* 1981a). This complex as well as complexes of the type $(\text{cod})\text{Rh}(\mu\text{-R-pyzt})_2\text{Rh}(\text{cod})$ ($\text{R} = \text{H}, \text{Me}, \text{Me}_2$) are shown to serve as catalysts for the hydroformylation of 1-heptene (Uson *et al* 1982b).

Red crystalline solids of the composition $\text{I}(\text{SCl})\text{Rh}(\mu\text{-R-N-N})_2\text{Rh}(\text{SCl})$ ($\text{I} = \text{Ph}_3\text{P},$



Scheme 2

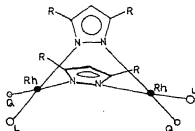


Figure 6. Structure of $\text{L}(\text{Q})\text{Rh}(\mu\text{-R}_2\text{-pyzt})_2\text{Rh}(\text{Q})\text{L}$.

alkaline methanol on $[\text{Rh}(\text{CS})(\text{R-N-NH})\text{L}_2]\text{ClO}_4$ in ether. Other methods to get these complexes involve the reaction of R-N-NH with $\text{RhCl}(\text{CS})\text{L}_2$ or $[\text{Rh}(\text{CS})\text{L}_2(\text{Me}_2\text{CO})_x]\text{ClO}_4$ in the presence of an alkali. The structure of the 3,5-Me₂-pyzt complex is confirmed by x-ray diffraction analysis (Uson *et al* 1982d) *vide* figure 6 ($\text{R} = \text{Me}$; $\text{Q} = \text{CS}$; $\text{L} = \text{Ph}_3\text{P}$). Thus the complexes $[(\text{PhO})_3\text{P}(\text{CO})\text{Rh}(\mu\text{-pyzt})]_2$ and $[\text{Ph}_3\text{P}(\text{SC})\text{Rh}(\mu\text{-3,5-Me}_2\text{-pyzt})]_2$ conceive almost the same geometry with an average Rh-N distance of 2.10 Å. The N-N bond length of the heterocycles is in the range 1.35–1.39 Å, and is slightly lengthened in the complexes when compared to that found for pyztH (1.35 Å; Berthou *et al* 1970). The two pyzt rings in both the complexes are planar and nearly perpendicular to each other; the angle formed by the two rings is 80.6° for the former whereas it is 82.3° for the latter. In both the cases the coordination around each metal atom is approximately square planar and the dihedral angle between the two square planes 86.2 (former) and 71.1° (latter) gives a bent configuration for the complex where the CO/CS and $(\text{PhO})_3\text{P}/\text{Ph}_3\text{P}$ ligands are in *trans*. For the former complex the intramolecular Rh-Rh distance is 3.568 Å as against 3.22 Å for the latter.

Powell *et al* (1982) have carried out oxidative addition reactions of $\text{L}(\text{OC})\text{Rh}(\mu\text{-R-pyzt})\text{Rh}(\text{CO})\text{L}$ with iodine or 1,2-diiodoethane. From these reactions they have isolated Rh(II) and Rh(III) (formal oxidation state) complexes of the formulae $\text{LI}(\text{OC})\text{Rh}(\mu\text{-3,5-Me}_2\text{-pyzt})_2\text{Rh}(\text{CO})\text{IL}$ ($\text{L} = (\text{PhO})_3\text{P}, \text{PhMe}_2\text{P}, \text{Ph}_2\text{MeP}, \text{PhMe}_2\text{As}$)

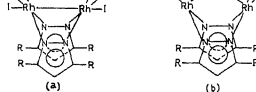


Figure 7. Proposed structures of
(a) $\text{LI}(\text{CO})\text{Rh}(\mu\text{-}3,5\text{-Me}_2\text{-pyzt})_2\text{Rh}(\text{CO})\text{IL}$ and
(b) $\text{LIRh}(\mu\text{-CO})(\mu\text{-R}_2\text{-pyzt})_2\text{RhIL}$ complexes.

and $\text{LIRh}(\mu\text{-CO})(\mu\text{-R-pyzt})_2\text{RhIL}$ ($\text{R} = 3,5\text{-Me}_2$; $\text{L} = \text{Ph}_3\text{P}$; $\text{R} = 3,5\text{-Ph}_2$; $\text{L} = \text{Ph}_2\text{MeP}$, Ph_2MeAs). While the Rh(II) complexes show IR bands in the range $2070\text{--}2000\text{ cm}^{-1}$ corresponding to terminal CO groups, the Rh(III) complexes exhibit an IR band at $ca\ 1790\text{ cm}^{-1}$ indicating bridging CO moiety. Based on IR and preliminary x-ray diffraction results the following structures have been proposed for the complexes (figure 7). In the solution, the Rh(II) complex ($\text{L} = \text{PhMe}_2\text{P}$) on standing for several days gets converted into Rh(III) complex. The latter complex is regarded as containing 16e with approximately square-pyramidal coordination around each metal atom. These observations support the remarkable stability of the heterocycles towards bridge cleavage reactions.

Reaction of complex IV with $\text{Pt}(\text{pyzt})_2\text{dppe}$ produces heterobinuclear complex, $[(\text{cod})\text{Rh}(\mu\text{-pyzt})_2\text{Pt}(\text{dppe})]\text{ClO}_4$ which undergoes displacement of cod with CO. One of the carbonyl groups in the resultant complex can be replaced by Ph_3P or $(\text{PhO})_3\text{P}$ (Uson *et al* 1981c). By contrast, Ph_3P instead of displacing CO, cleaves the heterocycle bridges in the ionic compound $[(\text{OC})_2\text{Rh}(\mu\text{-pyzt})_2\text{Pt}(\text{bipy})][\text{Rh}(\text{CO})_2\text{Cl}_2]$ which in turn is prepared by mixing complex II and $\text{Pt}(\text{pyzt})\text{bipy}$ in ether (Bandini *et al* 1979). Treatment of $[\text{Rh}(\text{CS})\text{L}_2(\text{Me}_2\text{CO})_x]\text{ClO}_4$ ($\text{L} = \text{Ph}_3\text{P}$, Cy_3P) with $\text{Au}(\text{pyzt})\text{Ph}_3\text{P}$ in $\text{Me}_2\text{CO-CH}_2\text{Cl}_2$ affords orange or pink crystals of $[\text{L}_2(\text{SC})\text{Rh}(\mu\text{-pyzt})\text{AuPPh}_3]\text{ClO}_4$ (Uson *et al* 1982d).

It may be noted that most of the above cited binuclear complexes invariably involve two of the exobidentate heterocycles. Perhaps location of the two nitrogen donor atoms of the heterocycle in adjacent positions and the fact that the heterocycle behaves as an anionic ligand necessitates the use of two such ligands for bridge formation.

8. Complexes containing 2,2'-bimidazolate and related heterocycles

Synthesis of the dinuclear complex $(\text{cod})\text{Rh}(\mu\text{-bimzt})\text{Rh}(\text{cod})$ by reacting $[(\text{cod})\text{Rh}(\mu\text{-OMe})]_2$ with bimztH_2 or $\text{Rh}(\text{cod})(\text{bimztH})$ in dichloromethane, has been reported by Rasmussen and coworkers (Kaiser *et al* 1976a). x-ray diffraction studies on the complex have indicated the planarity of the tetradentate bimzt dianion and the dihedral angle between the two rings, nearly 0° (as against $1\text{--}2^\circ$ for bimztH_2 ; Mitchell *et al* 1969). The geometry about each metal atom is approximately square-planar with the coordination polyhedron defined by two N atoms from bimzt ($\text{Rh-N} \sim 2.14\text{ \AA}$) and the midpoints of two olefin bonds from the cod ring (figure 8a). The cod groups are easily displaced on passing CO through a benzene solution of the above complex to give the tetranuclear complex $[(\text{OC})_2\text{Rh}(\mu\text{-bimzt})\text{Rh}(\text{CO})_2]_2$ which may also be prepared by treating

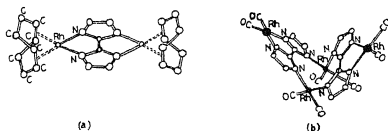


Figure 8. Structures of (a) $(\text{cod})\text{Rh}(\mu\text{-bimzt})\text{Rh}(\text{cod})$ and (b) $[(\text{OC})_2\text{Rh}(\mu\text{-bimzt})\text{Rh}(\text{CO})_2]_2$ complexes.

complex VIII with bimztH_2 . Crystal structure of this complex has been elucidated by x-ray diffraction analysis (Kaiser *et al* 1976b). It is found that each of the bimzt ligands coordinates simultaneously in a bidentate manner through both rings to one metal atom and also in a unidentate manner through each imidazolate ring to two metal atoms (figure 8b). The geometry about each rhodium is approximately squareplanar with the coordination polyhedron defined by two C atoms from CO groups and two N atoms from the bimzt groups; Rh-N distances are in the range 2.055–2.087 Å. The two rings of one bimzt ligand are nearly coplanar making a dihedral angle of 4° with each other. Metal-metal interactions of the bridging rhodium atoms (Rh-Rh = 2.975 Å) are thought to be the driving force toward the tetranuclear structure in preference to a dinuclear structure. It is also likely that changing the terminal ligand from cod to carbonyls has so modified the electron density on the rhodium atom that significant changes in molecular geometry are required to stabilise the system. Preparation of mixed-ligand complex $[(\text{cod})\text{Rh}(\mu\text{-bimzt})\text{Rh}(\text{CO})_2]_2$ has also been reported and the complex is expected to have structure similar to the aforesaid carbonyl.

Chloro complexes I and II react with the heterocycles, bpyztH_2 and mpyztH_2 in methanol to yield $\text{L}_2\text{ClRh}(\mu\text{-YH}_2)\text{RhClL}_2$ ($\text{L}_2 = \text{cod, nbd, tfb, (CO)}_2$; $\text{Y} = \text{bpyzt}$; $\text{L}_2 = \text{tfb, (CO)}_2$; $\text{Y} = \text{mpyzt}$) complexes. Addition of Et_3N to the above reaction systems, however, results in the formation of polynuclear complexes of the type $[\text{L}_2\text{Rh}(\mu\text{-Y})]_n$ ($\text{L}_2 = \text{cod, nbd, tfb, (CO)}_2$; $\text{Y} = \text{bpyzt, mpyzt}$). In the case of bpyzt complexes, the molecular weight measurements in chloroform indicate the value of n between 3 and 4. The dinuclear and polynuclear carbonyl complexes are also obtained by bubbling CO through dichloromethane solutions of the corresponding tfb containing complexes. Treatment of *trans*- $\text{RhCl}(\text{Ph}_3\text{P})_2$ ($\text{Q} = \text{CO}$), CS in benzene/toluene with alkaline methanolic solutions of bpyztH_2 also affords polynuclear complexes, $[(\text{Ph}_3\text{P})_2\text{QRh}(\mu\text{-bpyzt})]_n$ (νCO , 1990, 1970; νCS , 1290 cm^{-1}) (Uson *et al* 1982c).

Recently a report on the preparation of mixed-metal complexes of the composition $[\text{L}_2\text{Rh}(\mu\text{-Y})\text{Ru}(\text{Cp})\text{Ph}_3\text{P}]_n$ ($n = 1$ for $\text{L}_2 = \text{tfb}$; $\text{Y} = \text{bimzt, bbzlt}$; $\text{L}_2 = \text{cod, nbd, (CO)}_2$; $\text{Y} = \text{bbzlt}$; $n = 2$ for $\text{L}_2 = \text{nbd, (CO)}_2$; $\text{Y} = \text{bimzt}$) starting from $\text{RhL}_2(\text{acac})$ and $\text{Ru}(\text{Cp})(\text{YH})\text{Ph}_3\text{P}$ is made by Uson *et al* (1983a). Uson *et al* (1983b, 1983c) have also synthesised a wide range of hetero bi- and tri-nuclear cationic complexes of the formulae $[\text{L}_2\text{Rh}(\mu\text{-bbzlt})\text{M}(\text{dppe})]\text{ClO}_4$ ($\text{L}_2 = \text{cod, (CO)}_2, (\text{CO})(\text{Ph}_3\text{P})$; $\text{M} = \text{Pd, Pt}$), $[\text{L}_2\text{Rh}(\mu\text{-bbzlt})\text{Au}_2\text{Q}_2]\text{ClO}_4$ ($\text{L}_2 = \text{cod, (CO)}_2, (\text{CO})(\text{Ph}_3\text{P})$; $\text{Q}_2 = (\text{Ph}_3\text{P})_2, \text{dppe, ppm}$; $\text{L}_2 = (\text{CO})_2, (\text{CO})(\text{Ph}_3\text{P})$; $\text{Q} = (\text{MeO})_3\text{P}$) and $[\text{L}_2\text{Rh}(\mu\text{-bbzltH})\text{AuQ}]\text{ClO}_4$

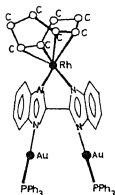


Figure 9. Structure of $[(\text{cod})\text{Rh}(\mu\text{-bbzlt})\text{Au}_2(\text{Ph}_3\text{P})_2]^+$ cation.

previously for similar complexes. The hetero trinuclear complex $[(\text{cod})\text{Rh}(\mu\text{-bbzlt})\text{Au}_2(\text{Ph}_3\text{P})_2]\text{ClO}_4 \cdot \text{CHCl}_3$ has been studied by x-ray crystallography (Uson *et al* 1983c). Accordingly the geometry around the Rh atom is approximately square-planar with the polyhedron defined by the two N atoms of bbzlt ($\text{Rh-N} \sim 2.1 \text{ \AA}$) and the midpoint of the two olefinic bonds of cod (figure 9). The two benzimidazole moieties of bbzlt ligand are slightly twisted and make a dihedral angle of 17.6° with each other.

9. Complexes containing 2-(2'-pyridyl)benzimidazole

The ligand pbzltH has features of a five-membered as well as a six-membered heterocycle. It reacts with complexes VII in dichloromethane to form $\text{Rh}(\text{diolefin})(\text{pbzlt})$ (diolefin = cod, nbd). Treatment of these mononuclear complexes, in stoichiometric amounts, with AuCl or L in the presence of AgClO_4 in acetone yields hetero dinuclear cationic complexes of the formula $[(\text{diolefin})\text{Rh}(\mu\text{-pbzlt})\text{ML}]\text{ClO}_4$ ($\text{M} = \text{Au}$; $\text{L} = \text{Ph}_3\text{P}$, $(\text{MeO})_3\text{P}$; $\text{M} = \text{Ag}$; $\text{L} = \text{Ph}_3\text{P}$). However, on reaction of the mononuclear complexes with only AgClO_4 in the mole ratio 2:1, trinuclear cationic complexes of the type $[(\text{diolefin})\text{Rh}(\mu\text{-pbzlt})\text{Ag}(\mu\text{-pbzlt})\text{Rh}(\text{diolefin})]\text{ClO}_4$ are formed. The mononuclear complexes also react with $\text{AuCl}(\text{tht})$ in dichloromethane to yield neutral complexes of the composition $(\text{diolefin})\text{Rh}(\mu\text{-pbzlt})\text{AuCl}$. In dichloromethane, the diolefin in the above complexes can be displaced by carbon monoxide to get the corresponding carbonyls (Uson *et al* 1983d).

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Abbreviations

acac	acetylacetonate
bzdzH ₂	1,6-bis(2'-benzimidazolyl)-2,5-dithiahexane
bzlt	2,2'-bibenzimidazolate dianion
bmzt	2,2'-biimidazolate dianion
bipy	2,2'-bipyridyl
pa	1,2-bis(4-pyridyl)acetylene
pe	1,2-bis(4-pyridyl)ethane
pel	1,2-bis(4-pyridyl)ethylene
pp	1,3-bis(4-pyridyl)propane
py	4,4'-bipyridyl

bpyzt	3,3',5,5'-tetramethyl-4,4'-bipyrazolate dianion
bzlt	benzimidazolate
cod	cycloocta-1,5-diene
Cp	cyclopentadienyl
dppe	1,2-bis(diphenylphosphino)ethane
dppm	1,1-bis(diphenylphosphino)methane
imzt	imidazolate
inzt	indazolate
mpyz	4,4'-methylene bis(3,5-dimethylpyrazolate) dianion
nbd	norborna-2,5-diene
ntd	1,8-naphthyridine
pbzltH	2-(2'-pyridyl)benzimidazole
phen	1,10-phenanthroline
phl	phthalazine
phz	phenazine
pyd	pyridazine
pym	pyrimidine
pyz	pyrazine
pyzt	pyrazolate
qux	quinoxaline
thf	tetrahydrofuran
tht	tetrahydrothiophen
tfb	tetrafluorobenzobarrelene

Metal ions in molecular association of porphyrins

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Abstract. Molecular association of porphyrins and their metal derivatives has been recognized as one of the important properties for many of their biological functions. The association is classified into (i) self-aggregation, (ii) intermolecular association and (iii) intramolecular association. The presence of metal ions in the porphyrin cavity is shown to alter the magnitudes of binding constants and thermodynamic parameters of complexation. The interaction between the porphyrin unit and the acceptor is described in terms of π - π interaction. The manifestation of charge transfer states both in the ground and excited states of these complexes is shown to influence the rates of excited state electron transfer reactions. Owing to paucity of crystal structure data, the time-averaged geometries of many of these complexes have been derived from magnetic resonance data.

Keywords. Metalloporphyrins; molecular association; charge transfer states; intramolecular interactions; intermolecular interactions; porphyrins.

Introduction

The widespread occurrence of porphyrins and their metal derivatives in many proteins and enzymes has stimulated considerable interest in the chemistry of these molecules. Metalloporphyrins lead to specific reactivity of hemoglobin, hemocytochromes and many oxidising enzymes. The available structural studies on a few heme proteins indicate strong evidence for the ubiquitous nature of molecular interactions between porphyrin π system and certain aromatic residues (Antonini and Brunni 1971; Abbot and Palfson 1974). This association of porphyrins with other aromatic molecules is of importance because of their involvement in redox catalysis (Castro *et al* 1977; Mannassen and Barllan 1970; Hill *et al* 1970; Dickerson 1972), their utility as models in the study of aromatic residue-porphyrin interaction in heme proteins, light-induced electron transfer in photosynthesis (Bradley and Calvin 1955; Seely 1966; Norris *et al* 1974; Sauer 1979; Clayton 1980) and herbicidal activity (Boon 1965). Moreover, many biological redox reactions are catalysed by metalloporphyrins and so an understanding of the role of charge transfer (CT) in these complexes is paramount. Much of the research in metalloporphyrins not only stems from their biological relevance but also arises from the search for new semiconductors, superconductors and conducting molecular crystals (Hoffman *et al* 1979, 1983). We present here a review of our work on the molecular complexation behaviour of porphyrins (both inter and intramolecular), the influence of metal ions on the stability of such complexes and the importance of the structures of these complexes in explaining their stabilities and reactivities. First we will examine the work that has been carried out on the complexation behaviour of naturally occurring porphyrins.

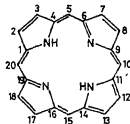
respectively, (c) they exhibit unique coordination chemistry *i.e.* the metal derivatives assume interesting stereochemistries and (d) they function both as a π -donor and π -acceptor towards diverse neutral organic molecules. Many of the biological functions involving porphyrins can be traced to either one or more of these features. Central to the understanding of these biological reactions is the relative ability of the porphyrins to associate among themselves and reversibly bind other neutral molecules (substrates) either for enzyme function or for substrate activation or for molecular conduction. It becomes essential then to define such associated products in terms of their stereochemistry and the nature of forces that govern the stabilisation of these products. The strength of association, equilibrium structure, stability and life-time of these complexes are different from system to system. Many factors, however, contribute to the strength of association and they are: the nature of the state of interacting molecules, geometry of the molecules under study, the media in which they are studied, temperature and others. The origin of these interactions has been discussed widely and has been the subject of considerable theoretical debate. Morakuma (1979) in an effort to arrive at the stabilising energy of these molecular systems, has partitioned the total energy of the system into various contributions: (a) electrostatic (b) polarization (c) exchange repulsion (d) charge transfer (e) coupling (f) electron correlation and (g) dispersion energies. The relative energies of these interactions often depend on the magnitudes of intermolecular separation and geometries of the associated molecules. The latter is of considerable importance since activation of molecules bound to the porphyrin or its metal derivatives critically depend on the position of contact and its orientation. A knowledge of these features becomes essential in the interpretation of enzyme function and also for the design of biomimetic models at the molecular level. Delineation of these features have been attempted at different levels. The electronic states of the porphyrins form the first level while the experimental demonstration of the existence of the molecular association followed by the structural elucidation of these complexes constitute the other levels.

2. Electronic structure of porphyrins

Porphyrins are tetrapyrrole pigments endowed with a number of peripheral positions available for substitution with other organic groups. A few porphyrins which occur in biological environments along with the synthetic ones are listed in table 1. The naturally occurring porphyrins are devoid of meso-substitution and carry propionic acid side chains. As shown below, the substituent groups do not alter the optical and emission properties of the porphyrinic core; however they induce considerable solvation effects and solubility characteristics.

Several theoretical treatments are available to describe the electronic structure of the porphyrins (Zerner and Gouterman 1960; Zerner *et al* 1966; Gouterman 1978; Dedieu *et al* 1982). The choice of the geometries becomes an important factor in such calculations. Somewhat idealised geometries with a four-fold symmetry (D_{4h}) have been used in these descriptions. A four-orbital model provides a comprehensive picture to explain many optical absorption and emission properties of the porphyrins. Considerations of π -electron calculations indicate that (a) in metalloporphyrins (D_{4h})

Table -1. Chemical structures of porphyrins.



PORPHYRIN	2	3	5	7	8	10	12	13	15	17	18	20
Etioporphyrin - I	Me	Et	H	Me	E	H	Me	Et	H	M	Et	H
Octaethylporphyrin	Et	Et	H	Et	Et	H	Et	Et	H	Et	Et	H
Mesoporphyrin - IX	Me	Et	H	Me	Et	H	Me	P	H	P	Me	H
	OH				OH							
Hematoporphyrin - IX	Me	CH ₃ Me	H	Me	CH ₃ Me	H	Me	P	H	P	Me	H
Protoporphyrin - IX	Me	V	H	Me	V	H	Me	P	H	P	Me	H
Uroporphyrin - I	A	P	H	A	P	H	A	P	H	A	P	H
Tetraphenylporphyrin	H	H	Ar	H	H	Ar	H	H	Ar	H	H	Ar
Coproporphyrin - I	Me	P	H	Me	P	H	Me	P	H	P	Me	H

Me = Methyl

Et = Ethyl

V = Vinyl

P = CH₂CH₂CO₂H

A = CH₂CO₂H

Ar = C₆H₅

the highest two occupied π -orbitals (a_{1u} and a_{2u}) are nearly degenerate and (b) the lowest unoccupied ($e_g\pi^*$) orbitals are degenerate. The optical absorption spectra of the porphyrins are characterised by an intense Soret absorption ($S_0 \rightarrow S_2$ transition) around 400 nm and Q bands (π - π transitions) in the region 500–650 nm. The relative intensities of the latter bands are often diagnostic of the nature of the substituents in the peripheral positions. It has been shown that the substituents do not alter the symmetry of the highest occupied and lowest unoccupied orbitals, though a marginal change in energies of these orbitals has been observed. Thus, the biologically active porphyrins exhibit absorption bands not too different from that of the synthetic ones *e.g.* 5,10,15,20 tetraphenyl porphyrin (TPP) and octaethyl porphyrin (OEP). For this reason, many studies utilise these porphyrins as biomimetic models.

The presence of metal ions in these porphyrins, however, induces considerable change in the geometries of the porphyrins and their orbital energies. Moreover, the perturbation of metal d electrons in the N_4 chromophore field alters the electronic structures of the porphyrins. Some of these features are listed in figure 1. It follows then, that the orbital energies and the stereochemistries can, in fact, dictate the electron donor and acceptor capacities of the metalloporphyrins. Moreover, the metal ions in the metalloporphyrins can themselves function as acceptors or donors towards other organic molecules. Thus, by changing the nature of metal ions in the porphyrin derivatives, it is possible to modulate the acceptor/donor properties of the porphyrins. It is for this reason, perhaps, the biological system chooses a few metal ions for their functional characteristics. Since the porphyrins are highly σ -donating bases and very weak π -acids, they increase the electron density on the metal ions typically, iron which leads to specific activity of hemoglobin and cytochromes. The porphyrins being extended π -system exhibit tendency to aggregate among themselves especially in solution. The solid state structures of a few porphyrins (Hoard 1975; Scheidt 1979) reveal that stacking of the porphyrin planes occur, though the interplanar separations are just above the van der Waal distances. The stability of the aggregated species is derived from incipient π - π interactions.

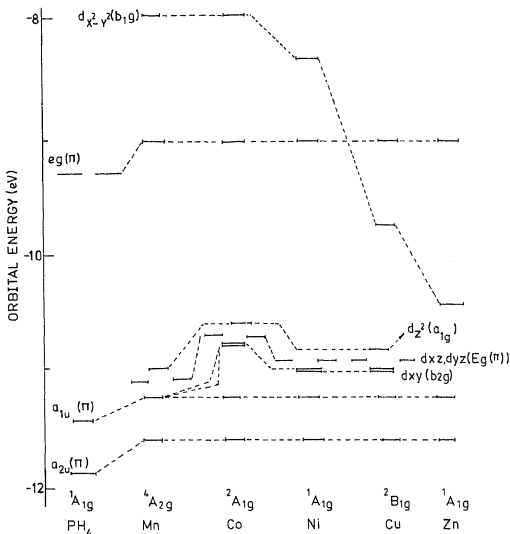


Figure 1. The energy levels of highest occupied and lowest unoccupied molecular orbitals of porphyrin dication and a few divalent metalloporphyrins. From Zerner and Gouterman (1960).

It is convenient to divide the molecular complexes formed by the porphyrins and their metal derivatives into two groups: intermolecular and intramolecular complexes. The intermolecular complexes can be further grouped to self-aggregated species and complexes formed between porphyrins and other neutral organic entities. The spectral features and the methods that have been used to characterise these species are different. A description of some of these features is given below.

3. Aggregation phenomena

Aggregation is a general feature of molecules endowed with extended π -systems. Both synthetic and naturally occurring porphyrins have been shown to form aggregated species. The extent of aggregation is limited by the nature of organic groups in the peripheral positions, concentration factors and the nature of solvent in which they are dissolved. It has been possible to study the aggregation features both by optical and magnetic resonance spectral methods. The optical absorption method has been used with advantage to determine the extent of aggregation and it is found that dimeric

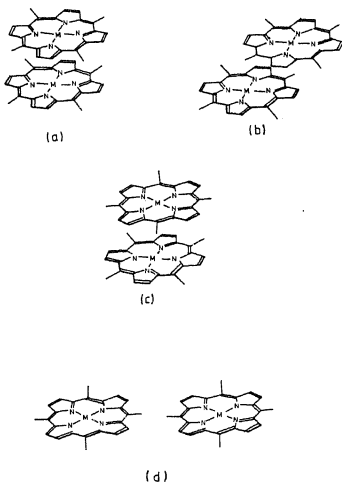


Figure 2. Possible geometries of porphyrin dimers (a) stacked (b) displaced (c) eclipsed and (d) linear.

White 1978). The dimerisation constant is found to be fairly high in the order of 10^5 to 10^6 . Addition of polar solvents seems to shift the equilibrium to monomer side. Despite the demonstration of the existence of aggregated species, no structural details are, however, available. In this connection it may be worthy to consider the magnetic resonance data. The ^1H NMR data of free-base coproporphyrins, mesoporphyrin, protoporphyrin and deuteroporphyrin IX dimethyl esters show a large dependence of the proton chemical shifts on increasing concentration of these porphyrins in solution (Abraham *et al* 1966; Janson and Katz 1972). The non-equivalence of proton resonances in concentrated solutions is taken as an evidence for the presence of aggregated species (Abraham *et al* 1973; Abraham and Swinton 1968; Doughty and Dwiggin 1969). Although the NMR method has provided the possible sites of the molecules in the monomer for the formation of aggregated species, the information obtained cannot unambiguously determine the extent of aggregation (dimer or higher order aggregates). The electron spin magnetic resonance data of Cu(II) porphyrin, however, has been interpreted in terms of a dimer (Blumberg and Peisach 1965). Aside, there has been no report concerning the structure of the dimers in solution. Several forms of dimer are possible (figure 2). Theoretical calculations on the energies of such dimers seem to indicate that face to face eclipsed configuration of the dimer is

noncovalently-linked crown porphyrin dimers have eclipsed geometries (Thanabal and Krishnan 1982a, b). A discussion of these aspects is dealt with under intramolecular association.

4. Intermolecular association

The electronic structure of the free-base porphyrins and their geometries are favourably poised to form numerous molecular complexes with various organic molecules. Most of the studies are directed towards the establishment of π - π interaction as a major source of stabilisation of molecular complexes formed between the porphyrin and other organic molecules. The enumeration of the nature of interactions has been the subject of many investigations. A few are directed towards the evaluation of binding constants and thermodynamic factors while others lay emphasis on the determination of structures of the molecular complexes. We shall critically examine some of these effects. Generally, optical absorption methods have been employed to evaluate binding constants while probes into the possible structures in solution are being made using magnetic resonance methods.

In a system containing an electron acceptor (A) and a donor (B) in equilibrium $A + D \rightleftharpoons AD$, the equilibrium constant (K) can be written as

$$K = [AD]/[A][D]. \quad (1)$$

Several methods are available in literature (Foster 1969) to evaluate the magnitudes of K . The value of K represents the binding constant of the two molecules in the associated state and the determination of K values at different temperatures essentially yields enthalpy (ΔH) and entropy change (ΔS) for the complexation process. In view of the very weak interactions that prevail in the associated state, it is anticipated that the values of K , ΔH and ΔS are small in magnitude. Evaluation of such parameters becomes an important component in determining the nature of forces that hold A and B in the associated state. The next question that arises is the manner in which the structure of the associated molecules is going to affect the magnitudes of these parameters. It has been suggested (Malini and Krishnan 1980) that in molecular complexing systems, the K values as determined represent the total stability (provided the concentration effects are taken care of) of the complex with respect to dissociation and the ΔH and ΔS values signify packing and orientation effects of the donors and acceptors in the complexes respectively. Thus, compatibility in sizes of the donor and acceptor, the planarity of the molecules and the symmetries of the orbitals (of donor and acceptor) for efficient overlap contribute to the magnitudes of the thermodynamic parameters. The strength of the complexes is related to the position of π absorption band and its intensity (Murrell 1959, 1961).

It would be fruitful at this stage to examine the different systems that have been studied and the results obtained thereof. Naturally occurring porphyrins form the first choice of study owing to their relevance in biological systems and their enhanced solubility in polar solvents. Mauzerall (1965) in his studies on coproporphyrins was able to characterise a few molecular complexes formed between the porphyrins and certain aromatic molecules and suggested that ionic and dispersion forces and in some cases π - π interactions are involved in the stabilisation of these complexes. The following

existence of molecular complexes; however, no structural information is available. The importance of molecular complex as an intermediate in certain biological reactions comes from the observation of increased denaturation of myoglobin by urea (Cann 1969) and enhanced rate of Zn(II) insertion into myoglobin in the presence of aromatic compounds (Cann 1965). In an effort to simulate the cyt P. 450 function of steroid hydroxylation, Hill *et al* (1973a) carried out an interesting study of the interaction of the Co(II), Fe(III), Ag(II) and Ni(II) derivatives of mesoporphyrin IX dimethyl ester with various steroids to find the possible site of location of the steroid over the porphyrin centre. This study constitutes the first experimental probe into solution structures of porphyrin complexes. The advantageous use of ^1H NMR and ESR methods have been exploited to arrive at the solution structures. Such studies reveal a family of structures for the complexes owing to randomization of molecules in solution and no specific interaction is discernible. However, they are able to point out the dominance of porphyrin ring interaction with steroids. The fruitfulness of such a study is borne out in the demonstration that metal ions do take part in binding (besides the porphyrin ring) especially in the interaction of caffeine and imidazole with porphyrins (Barry *et al* 1973).

Investigations on naturally occurring porphyrins and biologically important molecules, however, have certain limitations especially in view of their restricted solubility of these molecules in a range of non-polar solvents. Thus, use of organic molecules which essentially function as π -acceptors has been sought to delineate the structures and factors contributing to the stability of these complexes. The various acceptors that have been used are shown in figure 3. The studies utilising these acceptors

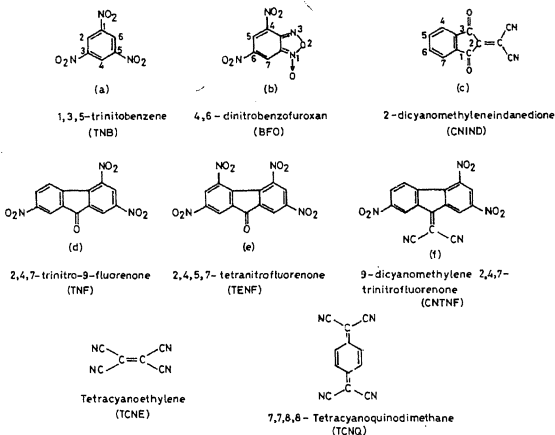
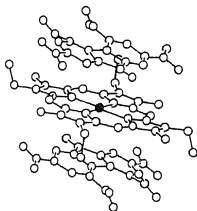


Figure 3. Chemical structures of various organic acceptors.

have yielded a wealth of information concerning the structures, factors contributing to the stabilities of the molecular complexes and the possible nature of interaction. First we will examine the interaction of some of these acceptors with naturally occurring porphyrins. Studies on the molecular complexes formed between mesoporphyrin dimethyl ester derivatives of Co(II) and Ni(II) with TNF and other nitroarenes deserve mention (Barry *et al* 1973; Hill *et al* 1967, 1973b). The use of Co(II) porphyrin as donor served as a dipolar probe in the ^1H NMR measurements to locate the protons of the acceptor molecule over the porphyrin core. Though they were able to arrive at two possible structures of the complexes, no unique structure has emerged from these studies. The absence of an unique structure in solution is probably due to the large size of the acceptor employed (TNF) which completely overlaps with the porphyrin core. Under these circumstances it would be difficult to perceive any preferential shielding and deshielding effects of the proton resonances of the acceptor (La Mar and Walker 1978). All the complexes thus far investigated presupposes 1:1 stoichiometry of the donor and acceptor and in a few cases this has been confirmed by optical and ^1H NMR methods. Only one structural report is available in literature (Grigg *et al* 1978). This relates to the 1:2 complex formed between Ni(II) derivative of etioporphyrin and tetranitrofluorenone (figure 4). It can be seen that fluorenone and porphyrin rings are approximately planar and the fluorenone ring is positioned in a fashion that its carbonyl group is nearest to the porphyrin plane at 2.97 Å. The Ni(II) atom is situated 3.39 Å from the mean plane of the fluorenone ring. This preliminary report is of importance especially with respect to the so far observed 1:1 stoichiometry in solution and the possibility of weak interaction between ketocarbonyl on Ni(II) ion. As would be expected later such interactions have not been detected in solution (Chandrashekar and Krishnan 1982).

Several synthetic porphyrins, TPP, substituted TPP, OEP and their metal derivatives have been employed as donors. The usage of these porphyrins has certain advantages in that they are relatively more soluble in a range of organic solvents than the naturally occurring porphyrins, a variety of substitutions is possible to delineate the effect of substituents on the molecular complexation characteristics and the influence of metal ions on the stability of these complexes could easily be studied. We shall now illustrate some of these aspects here. One of the desired objectives of the studies on molecular complexation of porphyrins is to determine any preferred orientation of the acceptor and donor in the associated species. The choice of small size acceptors (smaller in size relative to the size of porphyrin donor) is well suited for this kind of investigation. T



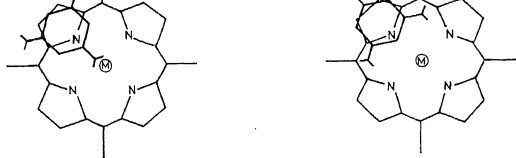


Figure 5. Possible geometries of porphyrin-TNB complex.

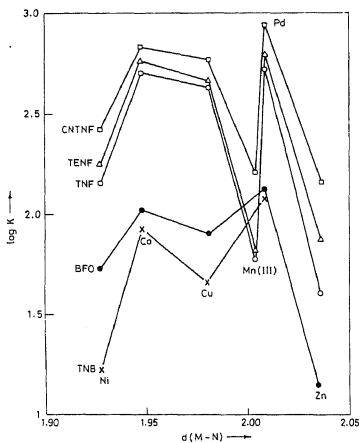
studies of La Mar *et al* (1974) and that of Fulton and La Mar (1976) are worthy of mention here. Based on the ^1H NMR results of Co(II) and Ni(II) porphyrin interaction with TNB, they were able to arrive at a possible structure of the molecular complex (figure 5). Moreover, it was pointed out that π -complexation of porphyrin with TNB alters σ binding framework of the porphyrin. Such changes brought out by the charge donation from the π -level of metalloporphyrin would in fact be accompanied with small changes in the orbital energies of these metal ions. An ESR study of these complexes involving metalloporphyrins (or spin-free metal ions) has revealed interesting features (Walker 1973, 1974; Hiroshiyoki and Iwaizumi 1980). Of particular interest is the manner in which the hyperfine tensors of the metalloporphyrins change on complexation with Lewis bases and aromatic π -acceptors. For example, it has been shown that axial ligation of the metal ion results in an increase in g values and decreases in $|A|$ values while the formation of a molecular complex leads to decrease in g values and increase in $|A|$ values. These changes have been useful in arriving at the M-N σ covalency as a consequence of π -donation to an acceptor. As we shall see later an increase in covalency factor relative to uncomplexed metalloporphyrin can be related to the electron affinity of the acceptor. Besides this, ESR study has been particularly helpful in the characterisation of charge-separated species [Co(III) TPP-TCNE] and TCNE^- and Co(III) TPP-TCNQ $^-$ (Wayland and Mohajer 1973; Konishi *et al* 1980). The interesting aspect being the formation of these species originates from molecular complexes in which donor porphyrin and acceptor exist in associated state.

A detailed description of molecular complexes formed by different metalloporphyrins (MTPPS) with diverse organic molecules is given in the work of Chandrashekar and Krishnan (1981, 1982, 1984a, b). The dominant theme in these studies is to relate the binding constants and thermodynamic parameters of complexation with the nature of metal ions, stereochemistries of the donor metalloporphyrins, ring size and electron affinity of the acceptors.

Interestingly, in all these systems, the donor function essentially rests with the porphyrin π manifold. The variation of metal ions in the porphyrin cavity results in the increased binding constants and for the interaction of any acceptor (TNB, TNF, TENF, BFO) with MTPPS, the binding constant varies as $\text{Co}^{2+} > \text{Cu}^{2+} > \text{VO}^{2+} > \text{Ni}^{2+} > 2\text{H} > \text{Mn}^{3+} > \text{Zn}^{2+}$. In a given group, however, the following order of stabilities holds good: $\text{Pd}^{2+} > \text{Ni}^{2+}$; $\text{Cd}^{2+} > \text{Zn}^{2+}$. This order of stabilities is quite different from that of Irving-Williams series proposed for coordinatively interacting systems. In order to find what parameters of the metal ions are responsible for this stability sequence, the

authors have examined the redox potential data, electronic configuration of metal ions and stereochemistries of the MTPPs. The first oxidation potentials of MTPPs signify the energy of the highest occupied molecular orbital (HOMO) and thus any π -donation is expected to originate from this level. The oxidation potential data of MTPPs follow the order: CoTPP > NiTPP > VOTPP $\sim$ TPP $\sim$ CuTPP $\sim$ ZnTPP (Felton 1978). This order, however, is not coincident with the observed order of stabilities. Since the binding constants only represent the stability with respect to dissociation, more appropriate parameters would be either the σ transition energy or the enthalpy change of complexation. As has been pointed out earlier (Gouterman and Stevenson 1962) the σ band in these molecular complexing systems could not be located with certainty owing to the intense bands of porphyrin π systems in the visible region. It is estimated that the position of γ_{CT} would be $15000\text{--}14000\text{ cm}^{-1}$ and it is not yet known with certainty the manner in which the position of this band is altered on changing the metal ions. The ΔH values for the interaction of various MTPPs with acceptors reveal not much change in any given order. Typically of ZnTPP interaction with acceptors, the K values are found to be much smaller, though the magnitudes of ΔH are much higher. A possible reason for this is attributed to the near-planarity of ZnTPP relative to other MTPPs. This brings in the importance of stereochemistries in governing the observed stability sequences.

It is easy to recognize that an ideal planar geometry (D_{4h}) would satisfy the condition of maximum overlap with the acceptor molecules thereby enhancing the stability, if there exists no specific site interaction. Possibly this provides an explanation for higher ΔH values observed for ZnTPP interaction. Any deviation from the stipulated



condition for the maximum overlap would immediately result in the lowered values of ΔH . In the case of transition metal derivatives of porphyrins [especially of VO(IV), Co(II), Cu(II), Ni(II) and others] there is an S_4 ruffling of the molecule departing from ideal planarity. A rough estimate of this departure could be depicted in terms of M-N distance (average). A plot of this parameter versus binding constant, however, showed no direct relation (figure 6). These arguments are rather too naive and a more reasonable approach would be to probe into d orbital energy levels of MTPPs and of their molecular complexes. Since, not much information about these aspects could be obtained from optical spectroscopy, the ESR data are worthy of consideration.

The detailed electronic energy levels are given in figure 1. Owing to the out-of-plane position of these metal ions, the d orbitals designation is as follows:

$$d_{x^2-y^2}; (b_1); d_{z^2}, (a_1); dxz, d_{yz}, (e); \text{ and } d_{xy}(b_2).$$

For the first row transition metal ions, the relative energies of these orbitals follow the order $a_1 > e > b_2$ which are nevertheless closely spaced. It can be recognized that an electron is in a_1 and b_2 orbitals for Co and VOTPP derivatives while a hole is present in b_1 in the case of CuTPP. Designating the orbital coefficients of b_1, a_1, e and b_2 as α, β, γ and δ , it is possible to estimate them from ESR hyperfine splittings. At this point we would like to seek how the magnitude of these coefficients varies on molecular complexation. Alternately one can approximate this by calculating 'unreduced energies' assuming the coefficients to be unity. This assumption should be followed with a caution that the coefficient should be multiplied by a factor 'orbital reduction factor'. Such a procedure when adopted for a series of analogous systems *viz.* molecular complexes formed by CuTPP with different π -acceptors of varying electron affinities, has given many useful information. The spin Hamiltonian for various systems is described in literature (Assour 1965; Manoharan and Rogers 1969) the covalency factor, α^2 can be calculated assuming that M-N bonds in MTPPs do not possess any in-plane or out-of-plane π bonding (Kivelson and Nieman 1961). The energies of the different orbitals calculated from g and A tensors for various CuTPP complexes are given in figure 7. It can be seen that $\Delta\alpha^2$, (change in covalency factor in the complex relative to CuTPP) varies linearly with the electron affinity of the acceptor. The decrease in α^2 value in the complexes indicates that M-N σ bond becomes more covalent. This can either arise from the increased electron density on nitrogens or an increase in the electronic charge on the copper in the complex relative to CuTPP. A similar observation has been made for VOTPP and CoTPP complexes.

The influence of solvents on the stabilities of these complexes has been investigated (Chandrashekar and Krishnan 1984a). It is demonstrated that solvents of high polarity decrease the binding constant values. Another point of interest emanating from these studies is the $^1\text{H NMR}$ study of BFO interaction with MTPPs (Chandrashekar and Krishnan 1984b). It has been found that though BFO is structurally related to TNB the possible site of location of BFO over the porphyrin is quite different from that of TNB in the molecular complex. The limiting proton chemical shifts experienced by different BFO protons are of the same magnitude indicating random positioning of BFO.

Besides, the stabilities of these molecular complexes, the major question that has not been answered is the extent to which CT contributes to the stabilities. Different lines of arguments have to be pursued since there exists no separate γ_{CT} band in the spectra of these complexes. A linear relation of K values *vs* electron affinity of the acceptors (figure

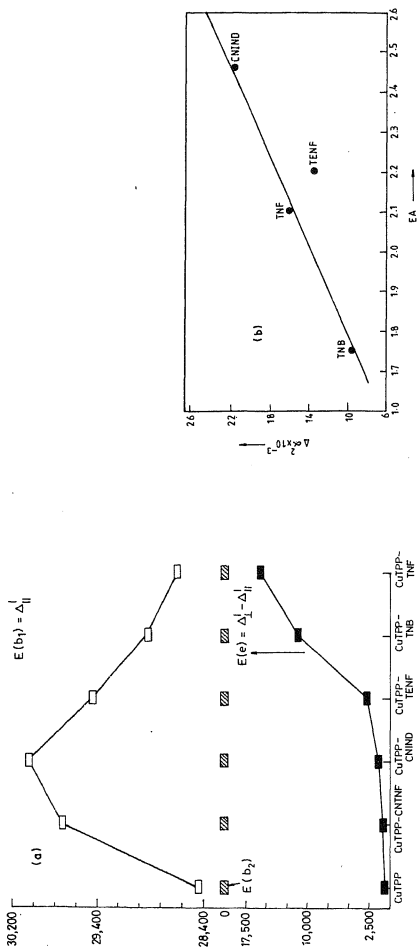


Figure 7. (a) Orbital energies of Cu(II) TPP complexes with various acceptors. (b) Linear dependence of $\Delta \epsilon^2$ with electron affinities of the selected acceptors.

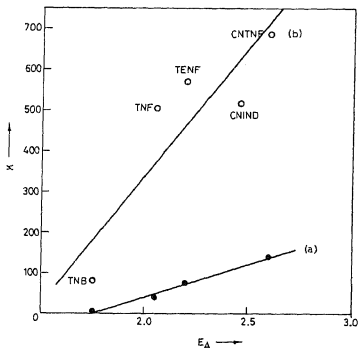


Figure 8. The dependence of stability constants of (a) Co(II) TPP and (b) ZnTPP complexes with various acceptors.

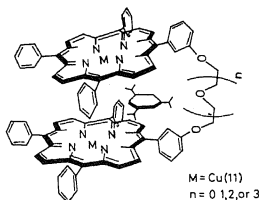
8) is not a sufficient condition to establish the CT contribution to the stability. In this context the interaction of Cu(II), Fe(III), Co(II) and Ni(II) derivatives of uroporphyrins and other metal (II) porphyrin derivatives with phenanthrolines is of interest (Shelnutt 1981, 1983a, b, c). Raman difference spectroscopy has been used in these studies. The metal-dependent frequency shifts are shown to be a sensitive function of the substituents in the phenanthroline acceptor. These studies further point out that ΔH values found in these systems are similar to those observed for other CT systems. These observations when interpreted in conjunction with the oxidation state-marker vibrations of metal porphyrin derivatives seem to indicate the existence of CT interactions.

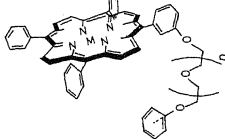
It would be fruitful at this state to enquire whether CT in the ground state of these complexes play any role in the excited states. It has been shown that nitroaromatics quench the singlet emission of Zn(II) derivatives of various porphyrin derivatives (Gouterman and Stevenson 1962; McCartin 1963; Whitten *et al* 1968; Lopp *et al* 1970; Chandrashekar and Krishnan 1981; Yamačá *et al* 1983). These studies reveal that singlet quenching occurs through the formation of a collisional complex. The observation that the rate of bimolecular quenching is fairly independent of the polarity of the solvents suggests the formation of an exciplex rather than a complete electron transfer. This is in contrast to the observation of Seely (1969) and the work on the corresponding complexes of chlorophyll analogues (Droupadi and Krishnan 1984). The formation of exciplexes in the study seems to derive support from the following observations (a) the concentration of the acceptors required to quench the singlet emission of porphyrins is much less than the concentration of the same acceptor required to decrease the absorbance of the donor porphyrin in the ground state and (b) absence of separate emission band of the complex. The latter though recognized as a necessary condition for the existence of an exciplex, the absence of this can be

intersystem crossing as observed in the TNB complex of anthracene (Kleinerman *et al* 1962).

4. Intramolecular association

The phenomenon of intramolecular association described in this section is distinct from that of self-association in a sense that the organic group involved in the molecular association originates from one of the peripheral positions, within the system. A study of these systems has important bearing in heme and cytochrome function, and in the primary charge separation in photosynthesis. Of systems of our present interest are the porphyrins. These can be classified into two groups: (a) covalently-linked bisporphyrins where the porphyrin unit is attached covalently (either singly or doubly) to another porphyrin moiety and (b) sidearm porphyrins where a porphyrin entity is covalently attached to another organic group (which can either function as an acceptor or a donor) through one of its peripheral positions. The basic question is what are the conditions under which one can obtain 'folded' conformer or whether folding of either one of the porphyrins (in the case of bisporphyrins) or the organic group (in the case of side arm porphyrins) over the porphyrin plane is a natural consequence of the omnipresent incipient π interaction? Secondly, what special advantages can be derived in the case of folded conformer *vis-a-vis* open conformers? Several synthetic model compounds have been designed (Wasielewski 1982). It appears that π interaction is a prerequisite for the exhibition of many photophysical properties *viz.* light-induced electron transfer singlet-singlet energy transfer and others. Though one can visualise such π interactions in the doubly-linked bisporphyrins, it is difficult to conceive this in the singly-linked bisporphyrins where there exists no steric constraints. Jeyakumar and Krishnan (1983) have suggested novel ways of folding two porphyrins through promotion of intramolecular π interaction. Interaction of a π -acceptor, TNB, with the singly-linked bisporphyrins is shown to result in the cooperative binding of two porphyrin planes mediated by a TNB molecule (figure 9). Several interesting consequences result from such studies. This suggests that π interaction is one of the dominant factors that govern the stabilities and the natural tendency of two extended π systems linked covalently would lead to folding depending on the inter-chromophore separation. Turning our attention to side arm porphyrins, several interesting compounds have been reported. The basic objective of such a study is not as much to elucidate π interaction but then to study intramolecular energy and electron transport. A variety of porphyrins





M = 2H, Co(II), Cu(II) and Zn(II)

Figure 10. Chemical structure of porphyrins endowed with podand side arm.

linked to quinones with methylene-ester groups (Kong *et al* 1982), methylene groups of variable length (Nishitani *et al* 1981), amides (Alan *et al* 1983; Siemiarczuk *et al* 1983) and porphyrins linked to mono and bisquinones and carotenoids (Moore *et al* 1980, 1982; Joshi *et al* 1982) have been reported. It is suggested in most of these compounds that intramolecular CT is responsible for many of the observed interesting photophysical properties. It is demonstrated that the natural tendency of porphyrins bearing an organic acceptor (figure 10) is to engage itself in the intramolecular CT interaction (Bhaskar Maiya and Krishnan 1983). This interaction, however, is critically dependent on the distance parameter which separates the organic acceptor from the porphyrin unit. The manifestation of intramolecular CT is also realized in a series of porphyrins appended with heterocyclic groups (Suriyanarayanan and Krishnan 1983). This has led to the increased singlet quantum yields indicating that the CT interaction is possibly present in the excited states as well.

Conclusion

This review presents a coherent picture of interactions that prevail in the molecular complexes involving porphyrins and their metal derivatives. Special emphasis can be laid on the following. The presence of metal ions in the porphyrin core is recognized to promote CT interaction, though more substantial evidence is necessary. The self-aggregation of porphyrins occur possibly through CT interaction; however, the energetics of such processes has not been completely understood. The CT interaction in the ground state seem to influence the excited-state properties. In a few cases it has been observed that CT interaction modulate the rate of excited state electron transfers from the singlet-excited state of the porphyrins to an acceptor. The covalently-linked porphyrin systems offer viable models to demonstrate the existence of CT interaction. The presence of these interactions is responsible for many interesting photophysical properties. It is hoped that in the near future many of these aspects would be understood in better terms especially in view of the tremendous importance the porphyrins bear in many biological reactions. Thus we expect this area of research to be continuing and a fruitful one.

Acknowledgements

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